National Institute for Health and Care Excellence

Draft

Heart valve disease presenting in adults: investigation and management

[H] Evidence review for transcatheter intervention, surgery or conservative management in heart valve disease

NICE guideline

Intervention evidence review underpinning recommendations 1.3.1, 1.5.1 to 1.5.13 and research recommendations in the NICE guideline

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Draft for consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1 Interventions

1.1 Review question: What is the clinical and cost-effectiveness of transcatheter intervention, surgery (with mechanical or biological valves) and conservative management compared with each other for adults with heart valve disease?

1.2 Introduction

Valve intervention can be performed with surgical or transcatheter approach, using a range of techniques and a range of types of prosthetic valves.

Surgical valve interventions comprise valve repair or valve replacement with a prosthetic mechanical or biological valve. Surgical valve repair restores the function of the patient's own valve, avoiding the need for replacement with a prosthetic valve; however, if the repair fails or the valve disease continues to progress, reintervention may be needed to replace the valve, with a surgical or transcatheter approach. Surgical valve replacement involves removal of the abnormal valve and replacement with a prosthetic valve. Mechanical prosthetic valves may last a lifetime, with no need for reintervention, however they need continuous anticoagulation to prevent clot forming on the valve and impairing the function of the valve or embolising in the arterial circulation resulting, for example, in a stroke. Furthermore, if they do need to be replaced again, the reintervention has to be again surgical, to remove the mechanical prosthetic valve and replace it with a new prosthesis. Surgical biological prosthetic valves degenerate usually several years after replacement and may need to be replaced again. However, the reintervention may be performed with a transcatheter approach, or if not feasible with a second heart operation.

Transcatheter valve interventions may allow for a quicker recovery after the procedure, if the procedure is uncomplicated, for example access for introduction of the catheter is straightforward and the patient does not require a pacemaker. The abnormal valve cannot be removed for a transcatheter valve "replacement", it is simply pushed aside to allow a prosthetic valve to be implanted within it. The transcatheter prosthetic valves are always bioprosthetic. As for surgical biological valves, the reintervention may be performed with a transcatheter approach (valve in valve). However, the transcatheter valves tend to degenerate faster than the surgical biological valves. Transcatheter valve "repair" reduces the abnormality of the valve function, however distorting the valve structure such that if reintervention is needed, this has to involve surgical replacement of the valve.

1.3 PICO table

For full details see the review protocol in 1.4.4.

Table 1: PICO characteristics of review question

Population	Adults 18 years and over presenting with heart valve disease requiring intervention, stratified by disease type as follows: • aortic stenosis (non-bicuspid) • aortic stenosis (bicuspid) • aortic stenosis (mixed non-bicuspid and bicuspid or unclear) • aortic regurgitation (non-bicuspid) • aortic regurgitation (bicuspid)

	• aortic regurgitation (mixed non-bicuspid and bicuspid or unclear) • mitral stenosis • mitral regurgitation • tricuspid regurgitation A threshold of 75% will be used to assign studies to the above strata. For example, to be assigned to the tricuspid regurgitation stratum, 75% of the population of a study would have to have tricuspid regurgitation as the type of heart valve disease driving the need for intervention. For populations with multiple valve disease, studies will be classified into strata based on the heart valve disease that drives the need for intervention (e.g. most severe valve disease). Only those undergoing their first intervention for heart valve disease (either surgical or transcatheter) will be included – studies where ≥10% of one or more of the groups have had previous attempts at surgical or transcatheter management prior to the trial will not be included. However, trials where patients have previously received medical management will not be excluded from this review. For studies where at least one of the arms is a replacement intervention, they will not be excluded if ≥10% had received a previous repair procedure but will be downgraded for indirectness. Exclusion: • Children (aged <18 years). • Adults with congenital heart disease (excluding bicuspid aortic valves). • Tricuspid stenosis and pulmonary valve disease. • Patients undergoing a second or greater number of surgical or transcatheter interventions for heart valve disease
Interventions	• Transcatheter repair • Transcatheter replacement with biological valves • Minimally invasive surgery repair • Minimally invasive surgery replacement with biological or mechanical valves • Standard surgery repair • Standard surgery replacement with biological or mechanical valves Note: Transcatheter intervention and surgical interventions will be stratified by repair and replacement. Within the replacement interventions, biological and mechanical valves will be pooled. Note: Sutureless valves will be included within both the standard and minimally invasive surgery interventions as reported in the studies Primary studies with a mixed intervention (some in the 'active' arm received the intervention of interest and some a different intervention) will be included if at least 90% received the intervention of interest.
Comparisons	Conservative management (for example, medical management/treatment or no treatment) Other active comparator listed above
Outcomes	**Primary:** • All-cause mortality at ≥12 months • Cardiac mortality at ≥12 months

	• Intervention-related mortality at 30 days • Health-related quality of life at ≥12 months • Onset or exacerbation of heart failure at ≥12 months • Intervention-related stroke or TIA at 30 days • Intervention-related major bleeding at 30 days • Need for re-intervention at ≥12 months **Secondary:** • Length of stay (following initial intervention) • Re-hospitalisation at ≥12 months • Intervention-related pacemaker implantation at 30 days • Intervention-related atrial fibrillation at 30 days • Intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication) • Prosthetic valve endocarditis at ≥12 months Follow-up: • Pool outcomes reported at the time-points specified above and take the latest reported time-point for the ≥12 months' time-point if multiple time points reported in a single study
Study design	Randomised controlled trials (RCTs) or systematic reviews of RCTs If no RCT data are available, observational data will not be considered for this review. This is due to the risk of confounding variables influencing the study results, reducing our confidence in the review results

1.4 Clinical evidence

1.4.1 Included studies

A total of 43 studies (from 127 papers) were included in the review; [1, 2, 4, 20, 28, 49, 57, 58, 60, 68, 74, 88, 100, 101, 106, 109, 110, 119, 120, 213, 214, 229, 232, 236, 247, 255, 258, 263, 266, 272, 274, 299, 311, 314, 322, 324, 347, 359, 367, 392, 399, 413, 429] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Tables 3-22).

Aortic valve disease

For aortic valve disease, the following studies were included for each stratum listed in the protocol:

- Aortic stenosis (non-bicuspid): n=10 studies covering comparisons between the following interventions: minimally invasive surgery replacement vs. standard surgery replacement (n=1)[229]; transcatheter replacement vs. standard surgery replacement (n=7)[2, 214, 232, 272, 311, 359, 392]; transcatheter replacement vs. pharmacological management (n=1)[213]; transcatheter replacement vs. surgical replacement (unclear/mixed invasiveness) (n=1)[299]

- Aortic stenosis (mixed non-bicuspid and bicuspid or unclear): n=5 studies covering comparisons between the following interventions: minimally invasive surgery replacement vs. standard surgery replacement (n=5)[20, 60, 68, 88, 324]

Note that no evidence was identified for the following aortic valve disease strata:

- Aortic stenosis (bicuspid)
- Aortic regurgitation (non-bicuspid)
- Aortic regurgitation (bicuspid)
- Aortic regurgitation (mixed non-bicuspid and bicuspid or unclear)

In addition to the pre-specified aortic valve disease strata, due to the limited number of studies identified for the various comparisons, the following evidence from populations with mixed/unclear aortic valve disease were included, which consisted of studies where there was a mixture of aortic stenosis and aortic regurgitation within the study (i.e. neither aortic stenosis nor aortic regurgitation made up ≥75% of the population) or studies where the population was only described as 'aortic valve disease' and the proportion of those with stenosis and regurgitation was not specified:

- Minimally invasive surgery replacement vs. standard surgery replacement (n=5)[58, 101, 263, 347, 413]

Mitral valve disease

For mitral valve disease, the following studies were included for each stratum listed in the protocol:

- Mitral stenosis: n=7 studies covering comparisons between the following interventions: minimally invasive surgery repair vs. standard surgery repair (n=1)[49]; transcatheter repair vs. standard surgery repair (n=2)[49, 314]; transcatheter repair vs. minimally invasive surgery repair (n=5)[28, 49, 255, 322, 399]; transcatheter repair vs. surgical repair (unclear/mixed invasiveness) (n=1)[74].

  Note the total for mitral stenosis does not add up to 7 as one study involved three different intervention arms and is therefore included under three of the above listed comparisons.

- Mitral regurgitation: n=8 studies covering comparisons between the following interventions: minimally invasive surgical repair vs. standard surgery repair (n=1)[266]; minimally invasive surgery (mixture of repair and replacement/) vs. standard surgery (mixture of repair and replacement) (n=1)[100]; surgical replacement (unclear/mixed invasiveness) vs. surgical repair (unclear/mixed invasiveness) (n=2)[1, 57]; transcatheter repair vs. pharmacological management (n=3)[274, 367, 429]; transcatheter repair vs. surgical repair/replacement (unclear/mixed invasiveness) (n=1)[120]; standard surgery replacement vs. standard surgery repair (n=1)[247].

In addition to the pre-specified mitral valve disease strata, due to the limited number of studies identified for the various comparisons, the following evidence from populations with mixed/unclear mitral valve disease were included, which consisted of studies where there was a mixture of mitral stenosis and mitral regurgitation within the study (i.e. neither mitral stenosis nor mitral regurgitation made up ≥75% of the population) or studies where the

population was only described as 'mitral valve disease' and the proportion of those with stenosis and regurgitation was not specified:

- Minimally invasive surgery replacement vs. standard surgery replacement (n=3)[109, 110, 236]

Tricuspid regurgitation

One study was identified that compared a transcatheter repair procedure + optimal medical treatment with optimal treatment alone for tricuspid regurgitation[106]. This study was extremely small with only 14 participants in each arm of the study.

Methodology

- **Mixed/unclear populations and interventions**: Evidence that came from mixed/unclear populations (for example mixed or unclear mitral valve disease populations) and/or mixed/unclear intervention strategies (for example, where the invasiveness of surgical strategy was not specified or where there was a mixture of repair and replacement procedures performed) were downgraded for indirectness, as the protocol for this review intended to stratify for the different populations and interventions and these studies did not fit accurately into the pre-specified categories.

- **Inconsistency:**

    - There were a number of outcomes where inconsistency was identified within meta-analyses – the majority of these were meta-analyses of only two or three studies so the pre-specified subgrouping strategies could not be performed. Random effects analysis was therefore used and the evidence downgraded due to inconsistency. Where Peto odds ratios had been used due to a small number of events or zero events, studies were not pooled and presented separately, as random effects is not possible when Peto odds ratios are used.

    - Similarly, subgrouping strategies for other meta-analyses with four or more studies could not explain heterogeneity as all studies fell within the same subgroup, for example for the age subgrouping strategy all had a population <75 years. In these cases, random effects analysis was used with downgrading for inconsistency.

    - For other meta-analyses with inconsistency, the studies did fall into separate subgroups (for example, studies could be separated into low, intermediate and high operative risk within the aortic stenosis non-bicuspid stratum), however the subgrouping strategies did not fully explain the heterogeneity, with high statistical heterogeneity values remaining within at least one of the subgroups. Again, in these cases random effects analysis was used with downgrading for inconsistency.

- **Sensitivity analysis:** Of the included studies, two did not present the raw number of events for each outcome and instead presented estimates of the event rate for each intervention using Bayesian analysis estimates[299, 311]. As this different method of reporting and analysing events may lead to differences in the results compared with similar studies, these results were included as reported but sensitivity analysis was

performed where relevant to remove these studies from the analysis for each outcome and determine whether the removal of the studies made a difference to the overall meta-analysis results. Both of these studies were included in the aortic stenosis (non-bicuspid) stratum.

One study[311] was meta-analysed with up to 6 other studies for 14 outcomes as part of the transcatheter replacement vs. standard surgery replacement comparison for this stratum. Overall, the removal of this study from the meta-analysis made no difference to the majority of the outcomes in terms of effect estimates. There were some differences for a number of outcomes, but as the analysis method was used across all outcomes and there was no reason to expect the different analysis method to affect some but not other outcomes, this study was retained within the meta-analyses for all outcomes.

The other study[299] that used this method of analysis and event reporting was the only study available for the comparison between transcatheter replacement and surgery replacement (unclear/mixed invasiveness). Therefore sensitivity analysis was not possible in this case.

- **Intervention-related mortality outcome:** Throughout the review this outcome was captured as all-cause mortality at 30 days, as the majority of studies only reported all-cause mortality, or it was difficult to determine which deaths were intervention-related and which were not.

- **Operative risk:** Although studies were not stratified by operative risk for analysis, operative risk for each study has been indicated within forest plots (low, intermediate, high or unclear operative risk)

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E:and GRADE tables in Appendix F:.

1.4.2 Excluded studies

Two Cochrane reviews related to this area were identified but excluded from the review[197, 202]. One was excluded because it was a meta-analysis of randomised controlled trials comparing transcatheter replacement with surgical replacement in people with aortic stenosis specifically in those at low operative risk[202] while this review aimed to pool all studies comparing these two interventions, regardless of operative risk. The other review was a meta-analysis of randomised controlled trials comparing limited sternotomy with full sternotomy for aortic valve disease[197] and was excluded as it pooled aortic stenosis and aortic regurgitation together, whereas our review aimed to look at evidence for these populations separately where possible, and it also excluded others types of minimally invasive procedure (mini-thoracotomies, port access, transapical, transfemoral or robotic procedures) that we did not wish to exclude in the protocol for this review. The reference lists of these reviews were however used to identify studies relevant for inclusion in this review.

See the excluded studies list in Appendix I:.

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1.4.8 Summary of clinical studies included in the evidence review

2 **Table 2: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Aortic stenosis (non-bicuspid), minimally invasive surgery replacement vs. standard surgery replacement				
Mächler 1999[229]	**Minimally invasive surgical replacement with biological or mechanical valve** (n = 60) L-shaped ministernotomy replacement with either CarboMedics (mechanical prosthesis) and Mosaic or Freestyle valves (bioprosthesis). Proportion of valve types used not stated. **Standard surgical replacement with biological or mechanical valve** (n = 60) Median sternotomy. 90% of people received mechanical prosthesis. 10% received bioprosthesis.	**Aortic stenosis (non-bicuspid)** (N = 120) Adults requiring aortic valve intervention for severe aortic stenosis. Some with regurgitation but majority (>75%) stenosis. Mean age: 65 (range: 31-77) Operative risk unclear Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease	All-cause mortality at 30 to 745 days Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Need for re-intervention at 30 days Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 1 year	Funding not stated
Aortic stenosis (non-bicuspid), transcatheter replacement vs. standard surgery replacement				
Adams 2014[2] Conducted in USA	**Transcatheter replacement with biological valves** (n = 394) Using the CoreValve device. Includes both iliofemoral and noniliofemoral routes with people randomised after stratification by approach.	**Aortic stenosis (non-bicuspid)** (N = 795) Adults with senile degenerative aortic stenosis (calcific) with an operative mortality at ≥15% at 30 days. NYHA class II or greater.	All-cause mortality at 5 years Cardiac mortality at 5 years Intervention-related mortality at 30 days Quality of life at 1 or 5 years Intervention-related stroke or TIA at 30 days	CoreValve trial Funded by Medtronic

Study	Intervention and comparison	Population	Outcomes	Comments
	After the procedure, people were started on aspirin 81mg daily and clopidogrel 75mg daily for 3 months, followed by monotherapy at the same dose indefinitely. **Standard surgical replacement with biological or mechanical valves** (n = 401) Conventional surgical technique. Choice of type and size of valve was left to the discretion of the operative surgeon. People were started on (at the least) aspirin 81mg daily after surgery to be continued indefinitely (including those requiring warfarin). Warfarin was started as indicated by guidelines.	Mean age: 83.2 (7.1) High operative risk: STS PROM intervention: 7.3 (3.0), STS PROM control: 7.5 (3.2). Logistic EuroSCORE intervention: 17.6 (13). Logistic EuroSCORE control: 18.4 (12.8). ~75% with coronary artery disease	Intervention-related major bleeding at 30 days Need for re-intervention at 5 years Re-hospitalisation at 5 years Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 5 years Major vascular complications at 30 days	
Leon 2016[214] Conducted in Canada and USA	**Transcatheter replacement with biological valves** (n = 1011) Using SAPIEN XT heart valve. The majority were performed by transfemoral route (76.3%) with the rest being performed transthoracically (23.7%).	**Aortic stenosis (non-bicuspid)** (N = 2032) People with senile degenerative aortic valve stenosis of NYHA class II or greater at intermediate operative risk. Mean age: 81.5 (6.7)	All-cause mortality at 5 years Cardiac mortality at 5 years Intervention-related mortality at 30 days Quality of life at 2 years Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days	PARTNER 2 trial Funded by Edwards Lifesciences

Study	Intervention and comparison	Population	Outcomes	Comments
	Standard surgical replacement with biological valve (n = 1021) Median sternotomy. Biological valves used in all patients. For both groups: all people received aspirin (91mg) and clopidogrel (≥300mg) after the procedure. Clopidogrel could be used for a minimum of 1 month, while aspirin should be continued indefinitely.	Intermediate operative risk: STS intervention: 5.8 (2.1) STS control: 5.8 (1.9) ~67-69% had concomitant coronary artery disease. Calcified aortic stenosis – non-calcified aortic valve disease was excluded.	Need for re-intervention at 5 years Length of hospital stay after intervention Re-hospitalisation at 5 years Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 5 years Major vascular complications at 30 days	
Mack 2019[232] Conducted in Australia, Canada, Japan, New Zealand and USA	**Transcatheter replacement with biological valves** (n = 503) Using a SAPIEN 3 system. Placed by transfemoral route. Started on aspirin 81mg and clopidogrel (>300mg) before the procedure and advised to continue taking it for at least 1 month. **Standard surgical replacement with biological valve** (n = 497) Median sternotomy approach in 75.7% of people. Minimally invasive approach in 24.3%. Biological valves were used.	**Aortic stenosis (non-bicuspid)** (N = 1000) Adults with severe, calcific aortic stenosis with an STS score <4. Mean age: 73.3 (5.8) Low operative risk: STS score intervention: 1.9 (0.7) STS score control: 1.9 (0.6) EuroSCORE II intervention: 1.5 (1.2) EuroSCORE II control: 1.5 (0.9) ~28% had concomitant coronary artery disease.	All-cause mortality at 1 year Cardiac mortality at 1 year Intervention-related mortality at 30 days Quality of life at 1 year Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Length of hospital stay after intervention Re-hospitalisation at 1 year Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 1 year	PARTNER 3 trial Funded by Edwards Lifesciences

Study	Intervention and comparison	Population	Outcomes	Comments
		Calcific aortic stenosis	Major vascular complications at 30 days	
Nielsen 2012[272] Conducted in Denmark	**Transcatheter replacement with biological valves** (n = 36) Using an Edwards SAPIEN valve. Approach by the transapical route. **Standard surgery replacement with biological valve** (n = 36) Median sternotomy approach. Using a PERIMOUNT aortic heart valve.	**Aortic stenosis (non-bicuspid)** (N = 59) Significant valvular aortic stenosis in adults older than 70 years (later increased to 75 years. Mean age: 80 (3.6) years Low operative risk: Logistic EuroSCORE intervention: 9.4 (3.9) Logistic EuroSCORE control: 10.3 (5.8). Concomitant coronary artery disease (requiring percutaneous coronary intervention or coronary artery bypass grafting) excluded Unclear if rheumatic or calcific disease	All-cause mortality at 5 years Cardiac mortality at 5 years Intervention-related mortality at 30 days Quality of life at 5 years Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Need for re-intervention at 30 days Length of hospital stay after intervention Intervention-related pacemaker implantation at 30 days Major vascular complications at 30 days	STACCATO trial Authors (non-principle) funded by Edwards Lifesciences
Reardon 2017[311] Conducted in Denmark,	**Transcatheter replacement** (n = 879)	**Aortic stenosis (non-bicuspid)** (N = 1746) Symptomatic, severe aortic stenosis at intermediate	All-cause mortality at 2 years months Cardiac mortality at 2 years	SURTAVI trial. Funded by Medtronic

Study	Intervention and comparison	Population	Outcomes	Comments
Germany, Netherlands, Switzerland and USA	Majority treated ileofemorally. Transcatheter replacement with biological valve. **Standard surgery replacement** (n = 867) Standard surgery replacement with biological valve. Dual antiplatelet therapy of aspirin and clopidogrel recommended for 3 months in both groups. Followed by lifelong monotherapy.	surgical risk (3-15% risk of 30-day surgical death) Mean age: 79.9 (6.2) years Operative risk: intermediate ~63-64% with concomitant coronary artery disease Unclear if rheumatic or calcific disease	Intervention-related mortality at 30 days Quality of life at 3 months – 2 years Intervention-related stroke at 30 days Intervention-related major bleeding at 30 days Need for re-intervention at 2 years Length of hospital stay after intervention Re-hospitalisation at 2 years Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Major vascular complications at 30 days	
Smith 2011[359] Conducted in Canada, Germany, USA	**Transcatheter replacement with biological valves** (n = 348) Using a SAPIEN heart valve system with either a transfemoral (244) or transapical (104) approach. **Standard surgical replacement with biological or mechanical valves** (n = 351) Median sternotomy approach. Type of valve used unclear.	**Aortic stenosis (non-bicuspid)** (N = 699) People with severe aortic stenosis and cardiac symptoms (NYHA class II-IV) who were considered as high surgical risk (STS score ≥10%). Mean age: 83.6 (6.8) years High operative risk: STS intervention: 11.8 (3.3) STS control: 11.7 (3.5)	All-cause mortality at 5 years Cardiac mortality at 5 years Intervention-related mortality at 30 days Quality of life at 1 year Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Length of hospital stay after intervention Re-hospitalisation at 5 years	PARTNER 1A trial Funded by Edwards Lifesciences

Study	Intervention and comparison	Population	Outcomes	Comments
	All people were started on dual antiplatelet therapy (aspirin and clopidogrel) for six months after the procedure.	Logistic EuroSCORE intervention: 29.3 (16.5) Logistic EuroSCORE control: 29.3 (15.6) ~75-77% with concomitant coronary artery disease Calcified aortic stenosis – non-calcified aortic valve disease was excluded.	Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 5 years Major vascular complications at 30 days	
Thyregod 2015[392] Conducted in Denmark and Sweden	**Transcatheter replacement with biological valves** (n = 145) Using a CoreValve system. Performed by a transfemoral approach. **Standard surgery replacement with biological valves** (n = 135) Conventional median sternotomy with bioprosthesis. All people advised to take clopidogrel (75mg once a day) for 3 months and aspirin (75mg once a day lifelong).	**Aortic stenosis (non-bicuspid)** (N = 280) Adults (70 years or older) with severe degenerative aortic stenosis with symptoms or without symptoms but with associated left ventricular systolic dysfunction and/or hypertrophy. Mean age: 79.2 (4.9) years Low operative risk: STS-PROM intervention: 2.9 (1.6) STS-PROM control: 3.1 (1.7) Logistic EuroSCORE intervention: 8.4 (4.0) Logistic EuroSCORE control: 8.9 (5.5)	All-cause mortality at 6 years Cardiac mortality at 5 years Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Need for re-intervention at 5 years Length of hospital stay after intervention Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 5 years Major vascular complications at 30 days	NOTION trial Individual authors are funded by Medtronic. Received funding from the Danish Heart Foundation.

Study	Intervention and comparison	Population	Outcomes	Comments
		Coronary artery disease requiring intervention was an exclusion criterion Unclear if calcific or rheumatic – calcific as it has been termed degenerative aortic stenosis?		
Aortic stenosis (non-bicuspid), transcatheter replacement vs. pharmacological management				
Leon 2010[213] Conducted in Canada, Germany and USA	**Transcatheter replacement with biological valves** (n = 179) Using Edwards SAPIEN heart valve system. Route used was transfemoral. **Conservative management – Pharmacological therapy** (n = 179) Standard therapy including pharmacological management and balloon aortic valvuloplasty (conducted in 140 people by 2 years). Route used for balloon aortic valvuloplasty was transfemoral.	**Aortic stenosis (non-bicuspid)** (N = 358) People with severe aortic stenosis and cardiac symptoms (NYHA class II-IV) considered at high risk of surgery. >10% of the people had previous surgical intervention (balloon aortic valvuloplasty) Mean age: 83.1 (8.6) Inoperable operative risk: STS score intervention: 11.2 (5.8) STS score control: 12.1 (6.1) Logistic EuroSCORE intervention: 26.4 (17.2) Logistic EuroSCORE control: 30.4 (19.1) ~68-74% had concomitant coronary artery disease.	All-cause mortality at 5 years Cardiac mortality at 5 years Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Need for re-intervention at 1 year Re-hospitalisation at 5 years Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 2 years Major vascular complications at 30 days	PARTNER 1B trial Funded by Edwards Lifesciences

Study	Intervention and comparison	Population	Outcomes	Comments
		Those requiring revascularisation excluded. Calcified aortic stenosis – non-calcified aortic valve disease was excluded.		
Aortic stenosis (non-bicuspid), transcatheter replacement vs. surgery replacement (unclear/mixed invasiveness)				
Popma 2019[299] Conducted in Australia, Canada, France, Japan, Netherlands, New Zealand and USA	**Transcatheter replacement with biological valves** (n = 734) Using one of three valve brands: CoreValve, Evolut R or Evolut PRO. Majority performed iliofemorally (99%). Pre-TAVR balloon valvuloplasty performed in 34.9% of people. Post-TAVR balloon dilation performed in 31.3% of people. Recommended to have 30 days or more of dual antiplatelet therapy followed by aspirin for 12 months. **Surgical replacement with biological valve** (n = 734) Type of procedure not clear (invasiveness unclear). Type of valve left to the surgeon's discretion, but all were biological valves	**Aortic stenosis (non-bicuspid)** (N = 1468) Symptomatic and asymptomatic people with severe (or very severe if asymptomatic) aortic stenosis considered to be at low risk for surgery (predicted mortality of <3% at 30 days). Mean age: 74.0 (5.9) Low operative risk: STS-PROM intervention: 1.9 (0.7) STS-PROM control: 1.9 (0.7) Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease	All-cause mortality at 2 years Cardiac mortality at 1 year Intervention-related mortality at 30 days Quality of life at 1 year Onset or exacerbation of heart failure at 1 year Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Need for re-intervention at 1 year Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 1 year Major vascular complications at 30 days	Evolut Low Risk Trial Funded by Medtronic

Study	Intervention and comparison	Population	Outcomes	Comments
	Recommended to be started on warfarin or aspirin after the procedure.			
Aortic stenosis (mixed non-bicuspid and bicuspid or unclear), minimally invasive surgery replacement vs. standard surgery replacement				
Aris 1999[20] Conducted in Spain	**Ministernotomy replacement with mechanical valve** (n = 20) 13 people underwent a reversed "L" ministernotomy. 7 people underwent a reversed "C" incision. All but 1 person in the entire study had a mechanical valve prosthesis. **Standard surgery replacement with mechanical valve** (n = 20) Median sternotomy. All but 1 person in the entire study had a mechanical prosthesis.	**Aortic stenosis (mixed bicuspid and non-bicuspid or unclear)** (N = 40) Consecutive people undergoing first-time elective, isolated aortic valve replacement (mixture of some with stenosis and some with regurgitation – 78% stenosis). Unclear whether bicuspid valve disease excluded. Mean age: 64 (11) Operative risk score intervention: 11.6 (5). Operative risk score control: 11.4 (5.5). Systolic function not stated. Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease	Cardiac mortality at 30 days Intervention-related mortality at 30 days Need for re-intervention at 30 days Length of hospital stay after intervention Intervention-related atrial fibrillation at 30 days	Funding not stated
Borger 2015[60] Conducted in Germany	**Minimally invasive surgical replacement with biological valves** (n = 51) Ministernotomy replacement with a biological valve.	**Aortic stenosis (mixed bicuspid and non-bicuspid or unclear)** (N = 100) People with aortic stenosis with or without aortic	All-cause mortality at 1 year Cardiac mortality at 1 year Intervention-related mortality at 30 days Quality of life at 3 months	CADENCE-MIS trial

Study	Intervention and comparison	Population	Outcomes	Comments
	Standard surgical replacement with biological valves (n = 49) Median sternotomy replacement with a biological valve.	insufficiency or low-to-moderate surgical risk requiring isolated aortic valve surgery. NYHA class II or greater. Mean age: 73.0 (5.3) Operative risk mixed: Low-to-moderate. Logistic EuroSCORE intervention: 6.4 (3.7) Logistic EuroSCORE control: 6.7 (3.6) Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease	Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Need for re-intervention at 30 days Intervention-related pacemaker implantation at 30 days Prosthetic valve endocarditis at 1 year	
Calderon 2009[68] Conducted in France	**Ministernotomy replacement with biological or mechanical valve** (n = 38) Reversed-L sternal incision. Does not state the type of valve used during the replacement. **Standard surgical replacement with biological or mechanical valve** (n = 39) Median sternotomy. Does not state the type of valve used during the replacement.	**Aortic stenosis (mixed bicuspid and non-bicuspid or unclear)** (N = 78) Adults (≥18 years) with aortic stenosis, ASA grade ≤3 with an LVEF >40%. Some with regurgitation rather than stenosis but majority (75%) stenosis. Mean age: 70.9 (11.4) Low operative risk: EuroSCORE intervention: 5.4 (1.9)	Cardiac mortality at 7 days Intervention-related mortality at 7 days Intervention-related major bleeding at 7 days Need for re-intervention at 7 days Length of hospital stay after intervention	Academic/government funding from the University Hospital of Bordeaux and the French Ministry of Research

Study	Intervention and comparison	Population	Outcomes	Comments
	For both groups, postoperative analgesia with patient controlled analgesia (morphine) with IV paracetamol and ketoprofen if insufficient relief achieved.	EuroSCORE control: 5.2 (1.8) Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease		
Dalén 2018[88] Conducted in Sweden	**Ministernotomy replacement with biological or mechanical valves** (n=20) Using partial J-shaped ministernotomy in the third intercostal space. 14 people had biological prosthesis. 5 had mechanical prostheses. 1 switched to the control group intraoperatively so valve type unknown. **Standard surgical replacement with biological or mechanical valves** (n = 20) Using median sternotomy. 16 people had a biological valve replacement. 5 had mechanical prostheses.	**Aortic stenosis (mixed bicuspid and non-bicuspid or unclear)** (N = 40) Adults with severe symptomatic aortic stenosis who were in sinus rhythm. Excluded if LVEF <45%. Mean age: 68.6 (8.5) Operative risk low: Mean EuroSCORE II 1.35 (0.79). Systolic function not stated. Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease	Cardiac mortality at 30 days Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Need for reintervention at 30 days Length of hospital stay after intervention Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days	CMILE trial Academic funding from Fredrick Lundberg and support from the Hirsch Fellowship.
Rodriguez-Caulo, 2020[324]	**Ministernotomy replacement with biological or mechanical valves** (n=50)	**Aortic stenosis (mixed bicuspid and non-bicuspid or unclear)** (N = 100)	Intervention-related mortality at 30 days Quality of life at 1 year	

Study	Intervention and comparison	Population	Outcomes	Comments
Conducted in Spain	Partial upper hemisternotomy extended into J-shape. All surgeons experienced in ministernotomy procedure. Completed in 94% with 3 converted to full sternotomy due to procedural difficulties. A total of 98% received a biological valve. **Standard surgical replacement with biological or mechanical valves** (n = 50) Full median sternotomy aortic valve replacement performed with conventional cardiopulmonary bypass. A total of 96% received a biological valve.	Adults with severe symptomatic aortic stenosis or double aortic lesion with predominant stenosis. Excluded if LVEF <40%. Mean age: 66-68 years in the two groups Logistic EuroSCORE I: 4-5% LVEF >60% in both groups Unclear if concomitant coronary artery disease Calcific disease	Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 72 h Need for reintervention at 30 days Length of hospital stay after intervention Intervention-related pacemaker implantation at 30 days Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 1 year	
Mixed/unclear aortic valve disease, minimally invasive surgery replacement vs. standard surgery replacement				
Ahangar 2013[4] Conducted in India	**Minimally invasive surgical replacement with biological or mechanical valves** (n = 30) Right anterolateral thoracotomy. A 35cm incision made in the right submammary fold starting at 35cm from the lateral border of the sternum. Entering through the third intercostal space. Type of valve used unclear	**Mixed/unclear aortic valve disease** (N = 60) People requiring aortic valve replacement (type of aortic valve disease unclear). Excludes people at high anaesthetic risk (ASA 3 or 4). Mean age: 38.5 (10.6) Operative risk unclear – high risk excluded Systolic function not stated	Length of hospital stay after intervention	No funding

Study	Intervention and comparison	Population	Outcomes	Comments
	Standard surgery replacement with biological or mechanical valves (n = 30) Conventional median sternotomy. For both groups, postoperative IV morphine (3mg four times a day) was given for analgesia. Oral anticoagulation with acenocoumarol was started on the second postoperative day (target INR 2.0-2.5). IV antibiotics (ceftriaxone/sulbactam and amikacin) were administered during hospital stay. Type of valve used unclear	Coronary artery disease exclusion criterion Unclear if rheumatic or calcific disease		
Bonacchi 2002[58] Conducted in Italy	**Ministernotomy replacement with mechanical or biological valves** (n = 40) Reversed-C incision in 15 people, reversed-L incision in 25 people. Using a 6-10cm midline skin incision started at the right border of the fourth-to-fifth intercostal space. Mentions both mechanical and biological valves. **Standard surgical replacement with biological or mechanical valves** (n = 40)	**Mixed/unclear aortic valve disease** (N = 80) People with aortic valve pathology (mixture of those with stenosis, regurgitation or both) who underwent aortic valve replacement. Mean age: 62.6 (9.5) Operative risk not stated Excludes people with significant systolic dysfunction (LVEF <0.25). Operative risk unclear.	Intervention-related mortality during hospital admission Intervention-related major bleeding during hospital admission Length of hospital stay after intervention Intervention-related atrial fibrillation during hospital admission	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
	Median sternotomy by a 20-25cm long midline skin incision from the sternal notch to the xiphoid appendage. Mentions both mechanical and biological valves.	Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease		
Dogan 2003[101] Conducted in Germany	**Minimally invasive surgery replacement** (n=20) Limited median skin incision (7-9 cm) and a reversed L-shaped upper partial sternotomy into 4th or 5th intercostal space. Type of valve unclear. **Standard surgery replacement** (n=20) Complete sternotomy. Valve type unclear.	**Mixed/unclear aortic valve disease** (N = 40) Patients scheduled for elective aortic valve surgery. Aortic stenosis (n=14), aortic insufficiency (n=4), combined (n=22) – mixture of types, no majority. Mean age: 65.7 (1.9) years Operative risk unclear Systolic dysfunction not stated Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease	Cardiac mortality (postoperative) Intervention-related mortality (postoperative) Intervention-related stroke or TIA (postoperative) Intervention-related major bleeding (postoperative) Length of hospital stay after intervention Intervention-related pacemaker implantation (postoperative)	Funding not stated
Fareed 2018[119]	**Minimally invasive surgical replacement with biological or mechanical valves** (n = 30)	**Mixed/unclear aortic valve disease** (N = 60)	Length of hospital stay after intervention	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
Conducted in Egypt	Limited upper ministernotomy to the third right intercostal space. Valve type not stated. **Standard surgical replacement with biological or mechanical valves** (n = 30) Median sternotomy replacement. Valve type not stated.	People with aortic valve disease (type not specified) requiring aortic valve replacement. Age not stated Operative risk unclear. Systolic function not stated Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease	Intervention-related atrial fibrillation at <3 months	
Moustafa 2007[258] Conducted in Egypt	**Ministernotomy replacement with mechanical valve** (n = 30) Reversed L-shaped ministernotomy from the sternal notch to the third intercostal space. Bicuspid St. Jude medical aortic valve prosthesis (mechanical). **Standard surgical replacement with mechanical valve** (n = 30) Median sternotomy replacement. Bicuspid St. Jude	**Mixed/unclear aortic valve disease** (N = 60) 50% of people had aortic stenosis, 50% had aortic regurgitation. People undergoing first-time elective aortic valve replacement. Mean age: 23.8 (3.49). Operative risk not stated. No systolic dysfunction, mean LVEF 55% (2.55%). Operative risk unclear.	Length of hospital stay after intervention	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
	medical aortic valve prosthesis (mechanical). Postoperative analgesia used: Tenoxicam 4g/12 hours while in ITU. Oral paracetamol (500mg) while on the ward.	Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease		
Nair 2018[263] Conducted in UK	**Ministernotomy replacement with biological or mechanical valve** (n = 118) Skin incised from half-way between the suprasternal notch and the sternal angle to the level of the fourth intercostal space, measuring approximately 8cm. Division of the manubrium in the midline from the suprasternal notch and then into the right fourth intercostal space. Mechanical and biological valves mentioned – majority biological. **Standard surgical replacement with biological or mechanical valves** (n = 104) Standard median sternotomy procedure. Mechanical and biological valves mentioned – majority biological. In both arms, a loading dose of 300 units/kg heparin followed by boluses of 5000 units to	**Mixed/unclear aortic valve disease** (N = 222) Adults undergoing first-time isolated aortic valve replacement (type of valve disease not stated). Mean age: 71.3 (12.3) Intermediate operative risk: Intervention: 5.9 (2.1). Control: 6.1 (2.1). No systolic dysfunction. Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease	All-cause mortality at 1 year Cardiac mortality at 1 year Intervention-related mortality at 6 weeks Quality of life at 1 year Need for re-intervention at 1 year Length of hospital stay after intervention	Academic/government funding from the National Institute of Health Research (NIHR).

Study	Intervention and comparison	Population	Outcomes	Comments
	achieve an activated clotting time above 450s.			
Shneider 2020[347] Conducted in Russia	**Ministernotomy replacement with biological or mechanical valve** (n = 56) J-shaped partial upper sternotomy, with 75% receiving mechanical valves and 25% receiving biological valves. Preoperative chest CT performed in all patients. **Standard surgical replacement with biological or mechanical valves** (n = 56) Standard median sternotomy procedure, with 69.6% receiving mechanical valves and 30.4% receiving biological valves. Preoperative chest CT performed in all patients.	**Mixed/unclear aortic valve disease** (N = 112) Adults aged 18-85 years with an indication for isolated aortic valve replacement (type of valve disease not stated). Mean age: 53.1 (14.9) and 56.1 (14.3) years in the two groups EuroSCORE II ~2 in both groups LVEF ~58% in both groups Unclear if concomitant coronary artery disease Unclear if rheumatic or calcific disease	All-cause mortality at 30 months Intervention-related mortality (in-hospital) Intervention-related stroke or TIA (early postoperative) Intervention-related major bleeding (postoperative) Need for re-intervention at 30 months Length of hospital stay after intervention Intervention-related pacemaker implantation (operative)	
Vukovic 2019[413] Conducted in Serbia	**Ministernotomy with biological or mechanical valves** (n = 50) Reverse J-shaped upper ministernotomy from the sternal notch to the third or fourth intercostal space. Biological	**Mixed/unclear aortic valve disease** (N = 100) People with aortic stenosis undergoing elective isolated aortic valve replacement (type of valve disease unclear).	All-cause mortality at 2 years Cardiac mortality at 2 year Intervention-related mortality at 30 days Intervention-related major bleeding at 30 days	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
	prostheses used in people older than 65 years. **Standard surgical replacement with biological or mechanical valves** (n = 50) Median sternotomy with a 20-25cm midline skin incision from the sternal notch. Biological prosthesis used in people older than 65 years.	Mean age: 65 (8.9) years Low operative risk: EuroSCORE II intervention: 1.87 (1.03) EuroSCORE II control: 1.98 (1.8) Unclear if concomitant coronary artery disease Unclear if calcific or rheumatic disease	Need for re-intervention at 30 days Length of hospital stay after intervention Re-hospitalisation at 2 years Intervention-related atrial fibrillation at 30 days Prosthetic valve endocarditis at 2 years	
Mitral stenosis, minimally invasive surgery repair vs. standard surgery repair				
Ben Farhat 1998[49] Conducted in Tunisia	**Transcatheter repair** (n=30) Balloon mitral commissurotomy. Performed with two pigtail balloons through a single interatrial septum puncture. **Standard surgery repair** (n=30) Open mitral commissurotomy. Performed by median sternotomy. Both commissures were incised. **Minimally invasive surgery repair** (n=30) Closed mitral commissurotomy performed through a left lateral thoracotomy. Both	**Mitral stenosis** (N = 90) Rheumatic, severe pliable mitral stenosis. Mean age: 29 (12) years. Included some under the age of 18. Morphology suitable for transcatheter intervention. Operative risk unclear. Unclear if concomitant coronary artery disease Rheumatic mitral valve disease	All-cause mortality at 7 years Cardiac mortality at 7 years Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Need for re-intervention at 7 years	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
	commissures could be correctly opened in 20 people. Before and after intervention, all people underwent right and left-sided cardiac catheterisation at rest.			
Mitral stenosis, transcatheter repair vs. standard surgery repair				
Ben Farhat 1998[49] Conducted in Tunisia	**Transcatheter repair** (n=30) Balloon mitral commissurotomy. Performed with two pigtail balloons through a single interatrial septum puncture. **Standard surgery repair** (n=30) Open mitral commissurotomy. Performed by median sternotomy. Both commissures were incised. **Minimally invasive surgery repair** (n=30) Closed mitral commissurotomy performed through a left lateral thoracotomy. Both commissures could be correctly opened in 20 people. Before and after intervention, all people underwent right and left-sided cardiac catheterisation at rest.	**Mitral stenosis** (N = 90) Rheumatic, severe pliable mitral stenosis. Mean age: 29 (12) years. Included some under the age of 18. Morphology suitable for transcatheter intervention. Operative risk unclear. Unclear if concomitant coronary artery disease Rheumatic mitral valve disease	All-cause mortality at 7 years Cardiac mortality at 7 years Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Need for re-intervention at 7 years	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
Reyes 1994[314] Conducted in India	**Transcatheter repair** (n = 30) Percutaneous balloon valvuloplasty. **Standard surgery repair** (n = 30) Open surgical commissurotomy by midline sternotomy	**Mitral stenosis** (N = 60) People (age 15-75 years) with severe rheumatic mitral stenosis. Mean age: 30 (9) years Morphology of mitral stenosis not stated Operative risk unclear. No history of other cardiac disease – coronary artery disease potentially excluded? Rheumatic mitral stenosis	All-cause mortality at 3 years Cardiac mortality at 3 years Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Intervention-related atrial fibrillation at 30 days	Academic funding (from the Institute of Medical Sciences, Nizam)
Mitral stenosis, transcatheter repair vs. minimally invasive surgery repair				
Arora 1993[28] Conducted in India	**Transcatheter repair** (n=100) Percutaneous balloon mitral valvuloplasty. Performed by transvenous transatrial route with a double-balloon technique. **Minimally invasive surgery repair** (n=100) Surgical closed mitral valvotomy. Performed by lateral thoracic approach.	**Mitral stenosis** (N = 200) Symptomatic people with moderate-to-severe rheumatic mitral stenosis. Mean age: 19.4 (5.47) years. Included some under the age of 18. Morphology suitable for transcatheter intervention. Operative risk unclear.	All-cause mortality at 22 months Cardiac mortality at 22 months Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Major vascular complications at 30 days	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
		Unclear if concomitant coronary artery disease Rheumatic mitral valve disease. More than minimal calcification of mitral valve an exclusion criterion.		
Ben Farhat 1998[49] Conducted in Tunisia	**Transcatheter repair** (n=30) Balloon mitral commissurotomy. Performed with two pigtail balloons through a single interatrial septum puncture. **Standard surgery repair** (n=30) Open mitral commissurotomy. Performed by median sternotomy. Both commissures were incised. **Minimally invasive surgery repair** (n=30) Closed mitral commissurotomy performed through a left lateral thoracotomy. Both commissures could be correctly opened in 20 people. Before and after intervention, all people underwent right and left-sided cardiac catheterisation at rest.	**Mitral stenosis** (N = 90) Rheumatic, severe pliable mitral stenosis. Mean age: 29 (12) years. Included some under the age of 18. Morphology suitable for transcatheter intervention. Operative risk unclear. Unclear if concomitant coronary artery disease Rheumatic mitral valve disease	All-cause mortality at 7 years Cardiac mortality at 7 years Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Need for re-intervention at 7 years	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
Momtahen 1997[255] Conducted in Iran	**Transcatheter repair** (n = 450) Balloon commissurotomy by a transseptal approach with a single balloon using the Inoue approach **Minimally invasive surgical repair** (n = 127) Surgical closed commissurotomy approached by left lateral thoracotomy.	**Mitral stenosis** (N = 577) Severe rheumatic mitral stenosis Mean age: 32 (range: 15-55) years. The majority of the population are women with a mean age of 32 years. Morphology suitable for transcatheter intervention. Operative risk unclear. Unclear if concomitant coronary artery disease Rheumatic mitral stenosis	All-cause mortality at during initial hospitalisation Cardiac mortality during initial hospitalisation Intervention-related stroke or TIA during initial hospitalisation Need for reintervention during initial hospitalisation	Funding not stated
Rifaie 2009[322] Conducted in Egypt	**Transcatheter repair** (n = 20) Percutaneous mitral valvotomy achieved through standard double balloon technique. **Minimally invasive surgery repair** (n = 20) Surgical commissurotomy. Left thoracotomy with a Tubb's dilator (opened to a maximum of 2.5cm in women and 3.5cm in men).	**Mitral stenosis** (N = 40) Moderate to severe rheumatic mitral stenosis with pulmonary congestion symptoms Mean age: 29.7 (7) years Morphology suitable for transcatheter intervention. Operative risk unclear. Those indicated for coronary artery bypass grafting	All-cause mortality at 8 years Cardiac mortality at 8 years Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Need for re-intervention at 8 years	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
	People in atrial fibrillation received oral anticoagulants for 6 weeks prior aiming for an INR of 2.0-3.0. This was stopped before the procedure so the INR decreased below 1.5.	excluded – unclear whether any had coronary artery disease that did not require intervention. Rheumatic mitral stenosis		
Turi 1991[399] Conducted in India	**Transcatheter repair** (n = 20) Balloon commissurotomy performed immediately after cardiac catheterisation. Used a double balloon technique. 9 people were taking digitalis, 16 were taking diuretics. **Minimally invasive surgery repair** (n = 20) Closed mitral commissurotomy by left lateral thoracotomy. 12 people were taking digitalis, 18 were taking diuretics.	**Mitral stenosis** (N = 40) People with severe rheumatic mitral stenosis (as determined by cardiac catheterisation) in sinus rhythm. Mean age: 27.1 (7.6) Morphology suitable for transcatheter intervention Operative risk unclear. Unclear if concomitant coronary artery disease Rheumatic mitral stenosis	All-cause mortality at 8 months Cardiac mortality at 8 months Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Intervention-related bleeding at 30 days Need for re-intervention at 8 months Major vascular events at 30 days	Equipment/drugs provided by industry
Mitral stenosis, transcatheter repair vs. surgical repair (unclear/mixed invasiveness)				
Cardoso 2002[74] Conducted in Brazil	**Transcatheter repair** (n = 40) Percutaneous balloon valvuloplasty performed through the transeptal route. Procedure performed by the Inoue technique.	**Mitral stenosis** (N = 80) Adults (age ≤60 years) with tight and pliable mitral stenosis of an NYHA class ≥2.	All-cause mortality at 2 years Cardiac mortality at 2 years Intervention-related mortality at 30 days Intervention-related major bleeding postoperatively	Funding not stated Same study also appears to have been reported on in Cardoso 2004 paper [73] at 5 year follow-up, however, the numbers

Study	Intervention and comparison	Population	Outcomes	Comments
	Surgical repair (unclear/mixed invasiveness) (n = 40) Open surgical mitral commissurotomy approached through median or right thoracotomy – mixed invasiveness.	Mean age: 32 (9) years. Morphology suitable for transcatheter intervention. Operative risk unclear. Unclear if concomitant coronary artery disease Rheumatic mitral stenosis	Need for re-intervention at 2 years Intervention-related pacemaker implantation postoperatively Intervention-related atrial fibrillation postoperatively Major vascular complications postoperatively	randomised differed between the two papers despite other features suggesting they were the same study. For this reason, outcomes were only extracted from the 2002 paper as it is unclear why in the numbers randomised differed in the 2004 paper.
Mitral regurgitation, standard surgery replacement vs. standard surgery repair				
Medved 2010[247] Conducted in Croatia	**Median sternotomy replacement with biological or mechanical valves** (n=40) Conventional median sternotomy valve replacement. Valve type not stated. **Median sternotomy repair** (n = 40) Conventional median sternotomy valve repair. Type of repair not specified.	**Mitral regurgitation** (N = 80) Adults (≥70 years) with mitral valve insufficiency (grades III-IV). 25 people required aortic valve replacement at the same time as mitral valve repair/replacement, and 27 people required tricuspid valve annuloplasty. Mean age: 76 (5) years. High operative risk (EuroScore): 15.76-16.94%. Unclear if concomitant coronary artery disease	Cardiac mortality at <30 days Intervention-related mortality at <30 days Intervention-related stroke or TIA at <30 days Need for re-intervention at <30 days Length of hospital stay after intervention	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
		Aetiology of mitral regurgitation was different for different patients: myxamatous, rheumatic, ischaemic or due to endocarditis		
Mitral regurgitation, minimally invasive surgery repair vs. standard surgery repair				
Nasso 2014[266] Conducted in Italy	**Minimally invasive surgery repair** (n = 80) Minithoracotomy (right anterolateral) in the inframammary groove. Working port in the third intercostal space, instrument port in the fifth-seventh intercostal spaces. Annuloplasty performed in all cases. **Standard surgery repair** (n = 80) Conventional median sternotomy repair. Annuloplasty performed in all cases. All people received intravenous ketorolac 30mg each day until the fourth postoperative day. They were subsequently started on indomethacin 50mg twice a day.	**Mitral regurgitation** (N = 160) Isolated, severe Barlow disease (bileaflet mitral prolapse) with an indication for elective repair. Mean age: 53.9 (10.6) years. Operative risk unclear. Degenerative mitral valve disease Concomitant coronary artery disease excluded	All-cause mortality at 3 years Intervention-related mortality at <30 days Quality of life at 3 years Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Need for re-intervention at 3 years Length of hospital stay after intervention Prosthetic valve endocarditis at 3 years	Funding not stated
Mitral regurgitation, minimally invasive surgery (mixed repair/replacement) vs. standard surgery (mixed repair/replacement)				
Dogan 2005[100]	**Minimally invasive surgery (mixed repair/replacement)** (n = 20)	**Mitral regurgitation** (N = 40)	Cardiac mortality during initial hospitalisation	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
Conducted in Germany	Minimally invasive surgery by right anterior thoracotomy (incision length = 5-7cm). **Standard surgery (mixed repair/replacement)** (n=20) Full median sternotomy. Replacement procedures were performed with preservation of the subvalvular apparatus. A temporary right ventricular pacing wire was placed in all people. All people were maintained on coumarin for the first 3 months after the operation, which was then discontinued if they were in sinus rhythm, or had a bioprosthetic valve replacement or valve repair.	Severe mitral valve disease (stenosis, regurgitation or both) schedules for elective mitral valve operation (>75% of the study population had mitral regurgitation). Mean age: 60.1 (12.3) years. Operative risk unclear. Aetiology of mitral regurgitation not reported Unclear if primary or secondary disease Haemodynamically significant coronary disease excluded Unclear if rheumatic or calcific disease Unclear if ischaemic or degenerative mitral regurgitation	Intervention-related mortality during initial hospitalisation Onset or exacerbation of heart failure in the postoperative period Intervention-related stroke or TIA in the postoperative period Intervention-related major bleeding in the postoperative period Intervention-related pacemaker implantation in the postoperative period	
Mitral regurgitation, surgical replacement (unclear/mixed invasiveness) vs. surgical repair (unclear/missed invasiveness)				

Study	Intervention and comparison	Population	Outcomes	Comments
Acker 2014[1] Conducted in Canada and USA	**Surgical repair (unclear/mixed invasiveness)** (n=126) Surgical valve repair with or without coronary artery bypass grafting. Performed with full or partial sternotomy or with a right thoracotomy – mixed invasiveness. Mitral valve repair accomplished using an approved rigid or semirigid undersized complete annuloplasty ring. **Surgical replacement with a biological or mechanical valve (unclear/mixed invasiveness)** (n=125) Surgical mitral valve replacement with or without coronary artery bypass grafting. Performed with full or partial sternotomy or with a right thoracotomy – mixed invasiveness. Type of valve selected based on surgeon preference. All participants received guideline-directed medical therapy by their treating cardiologist (including: aspirin, lipid-lowering agents, beta-blockers and ACE inhibitors).	**Mitral regurgitation** (N = 251) Adults with chronic, severe ischaemic secondary mitral regurgitation and coronary artery disease. Mean age: 69 (10) years. Operative risk not mentioned.	All-cause mortality at 2 years Intervention-related mortality at 30 days Quality of life at 1 year Onset or exacerbation of heart failure at 2 years Intervention-related stroke or TIA at 30 days Need for re-intervention at 2 years Length of hospital stay after intervention Prosthetic valve endocarditis at 2 years	Received academic or government funding

Study	Intervention and comparison	Population	Outcomes	Comments
Bogachev-Prokophiev 2017[57] Conducted in Russia	**Surgical replacement with biological or mechanical valve (unclear/mixed invasiveness)** (n = 44) Surgical replacement (unclear whether standard or minimally invasive) with the on-X prosthesis (mechanical). People who received a mechanical mitral valve were kept on lifelong anticoagulation with an INR target range 2.5-3.5. **Surgical repair (unclear/mixed invasiveness)** (n=44) Surgical repair (unclear whether standard or minimally invasive). Transaortic subvalvular apparatus interventions performed, including retracted secondary chordae cutting and abnormal papillary muscle release and/or resection. Low dose aspirin was prescribed post operatively in the repair group.	**Mitral regurgitation** (N = 88) Adults with hypertrophic obstructive cardiomyopathy with severe mitral regurgitation as defined by the European Society of Cardiology guidelines. Mean age: 50.8 (14.3) years Low operative risk (mean EuroSCORE II <4%). Unclear whether primary or secondary valve disease – secondary due to cardiomyopathy? Low operative risk Unclear if concomitant coronary artery disease Unclear if ischaemic or degenerative mitral regurgitation	All-cause mortality at 2 years Cardiac mortality at 2 years Intervention-related mortality at 30 days Intervention-related stroke or TIA at 30 days Intervention-related major bleeding postoperatively Need for re-intervention at 2 years Intervention-related pacemaker implantation in the early postoperative period Major vascular complications in the intraoperative period	Received academic or government funding
Mitral regurgitation, transcatheter repair vs. pharmacological management				

Study	Intervention and comparison	Population	Outcomes	Comments
Obadia 2018[274] Conducted in France	**Transcatheter repair** (n = 152) MitraClip percutaneous mitral valve repair by a femoral approach. People also received medical therapy: Single implantable cardioverter-defibrillation (48/151), cardiac resynchronisation therapy-defibrillator (46/151), ACE inhibitor/ARB (111/152), angiotensin receptor and neprilysin inhibitors (14/140), beta blockers (134/152), mineralocorticoid receptor antagonist (86/152), loop diuretic (151/152), oral anticoagulants (93/152). **Medical therapy alone** (n = 155) Single implantable cardioverter-defibrillation (57/152), cardiac resynchronisation therapy-defibrillator (35/152), ACE inhibitor/ARB (113/152), angiotensin receptor and neprilysin inhibitors (17/140), beta blockers (138/152), mineralocorticoid receptor antagonist (80/151), loop diuretic (149/152), oral anticoagulants (93/152).	**Mitral regurgitation** (N = 307) Adults (>18 years old) with severe secondary mitral regurgitation, NYHA class ≥2, LVEF 15-40%, and a minimum of one hospitalisation for congestive heart failure within 12 months of randomisation. Mean age: 70.1 (10.1) Inoperable: those considered suitable for mitral valve surgery by the heart team were excluded Secondary valve disease – ischaemic cardiomyopathy in 56-62% and non-ischaemic cardiomyopathy in 38-44% ~42-47% with previous coronary revascularisation	All-cause mortality at 2 years Cardiac mortality at 2 years Intervention-related mortality at 30 days Quality of life at 1 year Onset or exacerbation of heart failure at 2 years Intervention-related stroke or TIA during the periprocedural period Intervention-related major bleeding during the periprocedural period Major vascular complications during the periprocedural period	MITRA-FR trial Funded by Abbott Vascular

Study	Intervention and comparison	Population	Outcomes	Comments
Stone 2018[367] Conducted in Canada and USA	**Transcatheter repair** (n = 302) Transcatheter mitral valve repair with the MitraClip device. People were given intravenous antibiotics pre- and post-procedure. A loading dose of clopidogrel was given before the procedure and post-procedure antithrombotic therapy was achieved with either clopidogrel 75mg once a day and/or aspirin 81mg once a day for 6 months of longer. **Conservative management** (n = 312) Guideline-directed medical therapy as per each person's individual needs.	**Mitral regurgitation** (N = 614) Symptomatic secondary mitral regurgitation (3+ or 4+) due to cardiomyopathy of either ischaemic or non-ischaemic aetiology. NYHA functional class II, III or ambulatory IV and at least one hospitalisation for heart failure in 12 months prior to enrolment. Mean age: 71.7 (11.8) years Inoperable: to be included, cardiothoracic surgeon had to consider mitral valve surgery to be inappropriate Secondary valvular disease. ~43-49% with previous percutaneous coronary intervention and ~40% with previous coronary artery bypass grafting.	All-cause mortality at 2 years Cardiac mortality at 2 years Quality of life at 2 years Onset or exacerbation of heart failure at 2 years Intervention-related stroke or TIA at 30 days Need for re-intervention at 2 years Re-hospitalisation at 2 years	COAPT trial Funded by Abbott Vascular
Witte 2019[429] Conducted in Australia, France, Germany, Poland, Portugal, United Kingdom, USA	**Transcatheter repair** (n = 87) Mitral annual reduction. Coronary angiography performed and Carillon delivery catheter used to engage coronary sinus and implant device.	**Mitral regurgitation** (N = 120) Symptomatic secondary mitral regurgitation (2+, 3+ or 4+) despite stable (≥3 month) guideline-directed medical therapy	All-cause mortality at 1 year Intervention-related mortality at 30 days Quality of life at 1 year Onset or exacerbation of heart failure at 1 year Re-hospitalisation at 1 year	REDUCE-FMR trial Study funded by cardiac dimensions

Study	Intervention and comparison	Population	Outcomes	Comments
	Also received optimal heart failure medical therapy (optimally tolerated doses according to guidelines). **Conservative management** (n = 33) Received a sham procedure similar to that described above for transcatheter repair alongside optimal heart failure medical therapy (optimally tolerated doses according to guidelines).	Mean age: ~70 years in both groups Unclear whether the population is inoperable Secondary valvular disease.	Prosthetic valve endocarditis at 1 year	
Mitral regurgitation, transcatheter repair vs. surgery (mixed repair/replacement and unclear/mixed invasiveness)				
Feldman 2011[120] Conducted in Canada and USA	**Transcatheter repair** (n = 184) MitraClip device. Procedure performed through the femoral vein. After the procedure people receive aspirin 325mg once a day for 6 months and clopidogrel for 30 days. **Surgical repair (unclear/mixed invasiveness)** (n = 95) Mitral valve repair (86%) or replacement (14%). Method not stated explicitly.	**Mitral regurgitation** (N = 279) Moderate-severe or severe chronic mitral regurgitation in symptomatic people or asymptomatic people with additional features of severity (example: LVEF 25-60%, LVESD ≥40mm, new onset of AF). Mean age: 67.3 (12.8) years. Operative risk unclear. Mixture of primary and secondary disease - ~27% functional and ~73% degenerative	All-cause mortality at 5 years Intervention-related mortality at 30 days Quality of life at 1 year Intervention-related stroke or TIA at 30 days Intervention-related major bleeding at 30 days Need for re-intervention at 5 years Intervention-related atrial fibrillation at 30 days Major vascular complications at 30 days	EVEREST II trial Study funded by Abbott Vascular

Study	Intervention and comparison	Population	Outcomes	Comments
		~47% with concomitant coronary artery disease Unclear if rheumatic or calcific disease		
Unclear/mixed mitral valve disease, minimally invasive surgery replacement vs. standard surgery replacement				
El Ashkar 2016[110] Conducted in Egypt	**Minimally invasive surgical replacement with mechanical valve** (n = 17) Mitral valve replacement by small anterolateral, video-assisted minithoracotomy (incision size = 7-8cm). **Standard surgery replacement with mechanical valve** (n = 17) Mitral valve replacement by median sternotomy. Type of valve not explicitly mentioned.	**Mixed/unclear mitral valve disease** (N = 34) Isolated rheumatic mitral valve disease requiring mitral valve replacement (unclear proportion with stenosis and regurgitation). Mean age: 43.4 (11.41) years. Morphology of mitral stenosis not stated. Operative risk unclear. Aetiology of mitral regurgitation not stated. Coronary artery disease (ischaemic heart disease) an exclusion criterion Rheumatic mitral valve disease	Cardiac mortality during the initial hospitalisation Intervention-related mortality during the initial hospitalisation Length of hospital stay after intervention	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
El-Fiky 2000[109] Conducted in Egypt	**Port access replacement with biological or mechanical valve** (n = 50) Valve replacement (92%) or repair (8%) by a 10-12cm incision in the right submammary fold 3-5cm from the lateral sternal border with entry from the fourth intercostal space. Type of valve used unclear. **Standard surgical replacement with biological or mechanical valve** (n = 50) Valve replacement (94% or repair (6%) by a median sternotomy. Type of valve used unclear.	**Mixed/unclear mitral valve disease** (N = 100) Mitral valve disease. Majority had both stenosis and regurgitation with it being unclear which is driving the need for intervention. Some patients had congenital disease (<10%). Mean age: 22 (10) years. Majority of the patients in the study are women with a mean age of <45 years. Morphology of mitral stenosis not stated. Operative risk unclear. Aetiology of mitral regurgitation not stated. Concomitant coronary artery disease excluded Rheumatic aetiology in the majority of patients	Cardiac mortality during the initial hospitalisation Intervention-related mortality during the initial hospitalisation Length of hospital stay after intervention	Funding not stated
Malik 2015[236] Conducted in Pakistan	**Minimally invasive replacement with biological or mechanical valve** (n = 77) Right anterior thoracotomy. Procedure performed through the right submammary fold with access from the fourth intercostal space.	**Mixed/unclear mitral valve disease** (N = 281) People who underwent mitral valve replacement according to the ACC/AHA guidelines (type of valve disease not stated).	Intervention-related mortality in the postoperative period Intervention-related stroke or TIA in the postoperative period Need for reintervention in the postoperative period	No funding

Study	Intervention and comparison	Population	Outcomes	Comments
	Standard surgery replacement with biological or mechanical valves (n = 204) Procedure performed through median sternotomy approach. Both groups received acenocoumarol postoperatively with a target INR of 2.0-2.5.	Mean age: 28 (11) years. Morphology of mitral stenosis not stated. Operative risk unclear. Aetiology of mitral regurgitation not stated. Unclear if concomitant coronary artery disease Majority had rheumatic mitral valve disease	Length of hospital stay after intervention Prosthetic valve endocarditis at 2 years	
Tricuspid regurgitation, transcatheter repair vs. pharmacological management				
Dreger 2020[106] Conducted in Germany	**Transcatheter repair + medical treatment** (n = 14) Performed via right transfemoral venous access under local anaesthesia. Edwards SAPIEN XT valve implanted. All received oral anticoagulation following the procedure. Appears that optimal medical therapy (medical therapy recommended by current heart failure guidelines) also continued but this was unclear. **Medical treatment alone** (n = 14)	**Tricuspid regurgitation** (N=14) Severe symptomatic (NYHA class ≥II) tricuspid regurgitation and high surgical risk (logistic EuroSCORE I ≥15% or other contraindications for conventional valve surgery) Median age: 77 years in both groups Appears to be secondary tricuspid regurgitation as all had heart failure as well	All-cause mortality at 1 year Cardiac mortality at 1 year Intervention-related mortality (in-hospital) Quality of life at 3 months Onset or exacerbation of heart failure at 3 months Intervention-related major bleeding at 30 days Need for re-intervention at 48 h Re-hospitalisation at 1 year Major vascular complications at 30 days	TRICAVAL trial Study funded by Edwards Lifesciences

Study	Intervention and comparison	Population	Outcomes	Comments
	Optimal medical therapy (medical therapy recommended by current heart failure guidelines) continued.			

See Appendix D:for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

1.4.4.1 Aortic stenosis (non-bicuspid)

Table 3: Clinical evidence summary: Evidence not suitable for GRADE analysis

Study	Intervention and comparator	Outcome	Intervention results	Intervention group (n)	Comparator results	Comparator group (n)	Risk of bias
Leon 2016[214]	Transcatheter replacement vs. standard surgery replacement	Hospital length of stay	Median: 6 days	1011	Median: 9 days	1021	High
Mack 2019[232]	Transcatheter replacement vs. standard surgery replacement	Hospital length of stay	Median (IQR): 3 (2-3) days	496	Median (IQR): 7 (6-8) days	454	Very high
Smith 2011[359]	Transcatheter replacement vs. standard surgery replacement	Hospital length of stay	Median: 8 days	348	Median: 12 days	351	High

1 **Table 4: Clinical evidence summary: Minimally invasive surgery replacement vs. standard surgery replacement**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
All-cause mortality at ≥12 months	120 (1 study) 294 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.5 (0.26 to 8.66)	33 per 1000	16 more per 1000 (from 24 fewer to 253 more)
Cardiac mortality at ≥12 months	Not reported				
Intervention-related mortality at 30 days	120 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 7.39 (0.15 to 372.38)	0 per 1000	20 more per 1000 (from 30 fewer to 60 more)[c]
Health-related quality of life at ≥12 months	Not reported				
Onset or exacerbation of heart failure at ≥12 months	Not reported				
Intervention-related stroke or TIA at 30 days	120 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 7.39 (0.15 to 372.38)	0 per 1000	20 more per 1000 (from 30 fewer to 60 more)[c]
Intervention-related major bleeding (reoperation for bleeding) at 30 days	120 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b,d]	RR 1.67	50 per 1000	33 more per 1000 (from 29 fewer to 283 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
	postoperative	due to risk of bias, indirectness, imprecision	(0.42 to 6.66)		
Need for reintervention at ≥12 months (reoperation for paravalvular leakage)	120 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b,e] due to risk of bias, imprecision	OR 7.39 (0.15 to 372.38)	0 per 1000	20 more per 1000 (from 30 fewer to 60 more)[c]
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at ≥12 months	Not reported				
Intervention-related pacemaker implantation (pacing wire implantation) at 30 days	120 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.88 (0.47 to 1.63)	267 per 1000	32 fewer per 1000 (from 142 fewer to 168 more)
Intervention-related AF (supraventricular arrhythmias) at 30 days	120 (1 study) postoperative	⨁⨁⊖⊖ LOW[a,e] due to risk of bias, indirectness	RR 0.06 (0.01 to 0.46)	267 per 1000	251 fewer per 1000 (from 144 fewer to 264 fewer)
Intervention-related major vascular complications at 30 days	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
Prosthetic valve endocarditis at ≥12 months	120 (1 study) 294 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 7.65 (0.78 to 74.93)	0 per 1000	50 more per 1000 (from 10 fewer to 110 more)[c]

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c]Absolute effect calculated manually using risk difference as zero events in at least one arm of the study
[d]Downgraded by 1 increment as major bleeding that didn't require reoperation may not be captured in this outcome
[e]Downgraded by 1 increment as outcome defined as supraventricular arrhythmias, which could include events other than atrial fibrillation

Table 5: Clinical evidence summary: Transcatheter replacement vs. standard surgery replacement

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with transcatheter replacement (95% CI)
All-cause mortality at 12 months	1992 (3 studies) 2-6 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.07 (0.88 to 1.31)	148 per 1000	10 more per 1000 (from 18 fewer to 46 more)
All-cause mortality at 12 months (time-to-event)	4431 (4 studies) 1-5 years	⨁⨁⊖⊖ LOW[a,c] due to risk of bias, indirectness	HR 1.03 (0.93 to 1.13)	326 per 1000	8 more per 1000 (from 19 fewer to 34 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with transcatheter replacement (95% CI)
Cardiac mortality at 12 months	2697 (4 studies) 2-5 years	⨁⨁⨁⊖ MODERATE[b] due to imprecision	RR 1.12 (0.96 to 1.31)	162 per 1000	19 more per 1000 (from 6 fewer to 50 more)
Cardiac mortality at 12 months (time-to-event)	3732 (3 studies) 1-5 years	⨁⨁⊖⊖ LOW[a] due to risk of bias	HR 0.99 (0.85 to 1.15)	189 per 1000	2 fewer per 1000 (from 26 fewer to 25 more)
Intervention-related mortality at 30 days	6518 (7 studies) 30 days	⨁⨁⊖⊖ LOW[a,b] due to risk of bias, imprecision	RR 0.88 (0.66 to 1.16)	31 per 1000	4 fewer per 1000 (from 11 fewer to 5 more)
Quality of life (KCCQ summary) at 12 months - mix of change and final values Scale from: 0 to 100.	4493 (5 studies) 1-5 years	⨁⨁⊖⊖ LOW[a,d] due to risk of bias		The mean quality of life (KCCQ summary) at 12 months ranged across control groups from: 17.4-25.23 for change scores (n=4 studies) and 66.0-66.0 for final values (n=1 study)	The mean quality of life (KCCQ summary) at 12 months in the intervention groups was 1.09 higher (0.21 lower to 2.40 higher)
Quality of life (SF-12/SF-36 mental summary) at 12 months - mix of change and final values Scale from: 0 to 100.	2757 (5 studies) 1-5 years	⨁⨁⊖⊖ LOW[a,e] due to risk of bias		The mean quality of life (SF-12/SF-36 mental summary) at 12 ranged across control groups from 2.858-4.449 for change scores (n=3 studies) and 44-50.5 for final values (n=2 studies)	The mean quality of life (SF-12/SF-36 mental summary) at 12 months in the intervention groups was 0.33 lower (1.15 lower to 0.49 higher)
Quality of life at 12 months (SF-12/SF-36 physical summary) - mix of change	4133 (6 studies)	⨁⊖⊖⊖ VERY LOW[a,f,g]		The mean quality of life at 12 months (SF-12/SF-36 physical summary) ranged across control	The mean quality of life at 12 months (SF-12/SF-36 physical summary) in the intervention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with transcatheter replacement (95% CI)
and final values Scale from: 0 to 100.	3 months - 5 years	due to risk of bias, inconsistency		groups from: 2.716-5.598 for change scores (n=4 studies) and 33.2-42 for final values (n=2 studies)	groups was 0.49 higher (0.51 lower to 1.50 higher)
Quality of life (EQ-5D utility) at 12 months - mix of change and final values Scale from: 0 to 1.	4413 (5 studies) 3 months - 2 years	⨁⊖⊖⊖ VERY LOW[a,h,i] due to risk of bias, indirectness		The mean quality of life (EQ-5D utility) at 12 months ranged across control groups from 0.028-0.07 for change scores (n=4 studies) and 0.78-0.78 for final values (n=1 study)	The mean quality of life (EQ-5D utility) at 12 months in the intervention groups was 0 higher (0.01 lower to 0.01 higher)
Onset or exacerbation of heart failure at 12 months	Not reported				
Intervention-related stroke or TIA at 30 days	6518 (7 studies)	⨁⊖⊖⊖ VERY LOW [a,b,f] due to risk of bias, inconsistency, imprecision	RR 0.91 (0.0.60 to 1.37)	49 per 1000	4 fewer per 1000 (from 20 fewer to 18 more)
Intervention-related major bleeding at 30 days	6414 (7 studies)	⨁⊖⊖⊖ VERY LOW[a,b,f] due to risk of bias, inconsistency, imprecision	RR 0.51 (0.27 to 0.95)	253 per 1000	124 fewer per 1000 (from 13 fewer to 185 fewer)
Need for reintervention at 12 months (dichotomous)	2760 (4 studies) 30 days - 5 years	⨁⨁⊖⊖ LOW[a] due to risk of bias	RR 4.95 (2.34 to 10.45)	6 per 1000	24 more per 1000 (from 8 more to 57 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with transcatheter replacement (95% CI)
Need for reintervention at 12 months (time-to-event)	2032 (1 study) 5 years	⨁⨁⊖⊖ LOW[a] due to risk of bias	HR 3.28 (1.32 to 8.15)	6 per 1000	13 more per 1000 (from 2 more to 41 more)
Length of stay post-intervention	2002 (3 studies)	⨁⊖⊖⊖ VERY LOW[a,b,f,j] due to risk of bias, inconsistency, imprecision		The mean length of stay post-intervention ranged across control groups from 7.6-12.9 days	The mean length of stay post-intervention in the intervention groups was 2.41 days lower (5.33 lower to 0.51 higher)
Rehospitalisation at 12 months	3109 (3 studies) 2-5 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.34 (1.16 to 1.55)	159 per 1000	54 more per 1000 (from 25 more to 87 more)
Rehospitalisation at 12 months (time-to-event)	2982 (2 studies) 1-5 years	⨁⊖⊖⊖ VERY LOW[a,b,f,k] due to risk of bias, inconsistency, indirectness, imprecision	HR 0.94 (0.49 to 1.82)	175 per 1000	10 fewer per 1000 (from 85 fewer to 120 more)
Intervention-related pacemaker implantation at 30 days	6432 (7 studies)	⨁⨁⊖⊖ LOW[a,f] due to risk of bias, inconsistency	RR 2.43 (1.39 to 4.25)	57 per 1000	82 more per 1000 (from 22 more to 185 more)
Intervention-related AF at 30 days	6198 (6 studies)	⨁⨁⊖⊖ LOW[a,f]	RR 0.31 (0.24	329 per 1000	227 fewer per 1000 (from 194 fewer to 250 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with transcatheter replacement (95% CI)
		due to risk of bias, inconsistency	to 0.41)		
Major vascular complications at 30 days	6438 (7 studies)	⨁⨁⨀⨀ LOW [a,f] due to risk of bias, inconsistency	RR 2.82 (1.77 to 4.49)	28 per 1000	51 more per 1000 (from 22 more to 98 more)
Prosthetic valve endocarditis at 12 months	4711 (5 studies) 1-5 years	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision	RR 1.29 (0.85 to 1.96)	16 per 1000	5 more per 1000 (from 2 fewer to 15 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[c]Downgraded by 1 increment as one study included >10% of participants that had received previous aortic valve repair. Also, another study included <25% that had minimally invasive rather than standard surgical replacement.

[d]MIDs used to address imprecision were ±10.91

[e]MIDs used to address imprecision were ±3.00

[f]Downgraded by 1 increment as heterogeneity is present that cannot be explained by subgroup analysis.

[g]MIDs used to address imprecision were ±2.00

[h]Downgraded by 1 increment as one study included >10% of participants that had received previous aortic valve repair. Also, another study only had 3 months follow-up for this outcome.

[i]MIDs used to address imprecision were ±0.03

[j]MIDs used to address imprecision were ±4.015

[k]Downgraded 1 by increment as <25% of the surgery arm received minimally invasive surgery rather than standard surgery

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1 **Table 6: Clinical evidence summary: Transcatheter replacement vs. pharmacological management**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with pharmacological management	Risk difference with transcatheter replacement (95% CI)
All-cause mortality at 12 months	358 (1 study) 5 years	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, indirectness	HR 0.5 (0.39 to 0.64)	832 per 1000	242 fewer per 1000 (from 151 fewer to 331 fewer)
Cardiac mortality at 12 months	358 (1 study) 5 years	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, indirectness	HR 0.41 (0.31 to 0.54)	659 per 1000	302 fewer per 1000 (from 218 fewer to 375 fewer)
Intervention-related mortality at 30 days	358 (1 study) 30 days	⨁⨀⨀⨀ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.8 (0.62 to 5.27)	28 per 1000	22 more per 1000 (from 11 fewer to 120 more)
Health-related quality of life at 12 months	Not reported				
Onset or exacerbation of heart failure at 12 months	Not reported				
Intervention-related stroke or TIA	358 (1 study) 30 days	⨁⨀⨀⨀ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 4 (1.15 to 13.93)	17 per 1000	51 more per 1000 (from 3 more to 220 more)
Intervention-related major bleeding	358 (1 study) 30 days	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, indirectness	RR 4.29 (1.93 to 9.5)	39 per 1000	128 more per 1000 (from 36 more to 331 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with pharmacological management	Risk difference with transcatheter replacement (95% CI)
Need for reintervention at 12 months	358 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	RR 0.06 (0.02 to 0.14)	486 per 1000	457 fewer per 1000 (from 418 fewer to 476 fewer)
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at 12 months	358 (1 study) 5 years	⨁⨁⊖⊖ LOW[a,b] due to risk of bias, indirectness	HR 0.4 (0.29 to 0.55)	531 per 1000	270 fewer per 1000 (from 190 fewer to 334 fewer)
Intervention-related pacemaker implantation at 30 days	358 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.67 (0.24 to 1.83)	50 per 1000	16 fewer per 1000 (from 38 fewer to 42 more)
Intervention-related AF at 30 days	358 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	OR 0.51 (0.05 to 4.95)	11 per 1000	5 fewer per 1000 (from 10 fewer to 41 more)
Major vascular complications	358 (1 study) 30 days	⨁⨁⊖⊖ LOW[a,b] due to risk of bias, indirectness	RR 14.5 (3.51 to 59.86)	11 per 1000	148 more per 1000 (from 28 more to 647 more)
Prosthetic valve endocarditis at 12 months	358 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 3 (0.32 to 28.57)	6 per 1000	12 more per 1000 (from 4 fewer to 165 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with pharmacological management	Risk difference with transcatheter replacement (95% CI)

[b]Downgraded by 1 increment as >10% of participants had previous surgical intervention (balloon aortic valvuloplasty)
[c]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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2 **Table 7: Clinical evidence summary: Transcatheter replacement vs. surgery replacement (unclear/mixed invasiveness)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgery replacement (unclear/mixed invasiveness)	Risk difference with transcatheter replacement (95% CI)
All-cause mortality at 12 months	1468 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1 (0.62 to 1.6)	45 per 1000	0 fewer per 1000 (from 17 fewer to 27 more)
Cardiac mortality at 12 months	1468 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.68 (0.34 to 1.38)	26 per 1000	8 fewer per 1000 (from 17 fewer to 10 more)
Intervention-related mortality at 30 days	1468 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	OR 0.42 (0.15 to 1.21)	14 per 1000	8 fewer per 1000 (from 12 fewer to 3 more)
Quality of life (KCCQ summary) at 12 months Scale from: 0 to 100.	778 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, indirectness		The mean quality of life (KCCQ summary) at 12 months in the control groups was 90.8	The mean quality of life (KCCQ summary) at 12 months in the intervention groups was 0.5 lower (2.27 lower to 1.27 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgery replacement (unclear/mixed invasiveness)	Risk difference with transcatheter replacement (95% CI)
Onset or exacerbation of heart failure at 12 months	1468 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.5 (0.31 to 0.81)	65 per 1000	32 fewer per 1000 (from 12 fewer to 45 fewer)
Intervention-related stroke or TIA (all stroke) at 30 days	1468 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1 (0.58 to 1.72)	34 per 1000	0 fewer per 1000 (from 14 fewer to 24 more)
Intervention-related stroke or TIA (TIA) at 30 days	1468 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	OR 1 (0.25 to 4.01)	5 per 1000	0 fewer per 1000 (from 4 fewer to 15 more)
Intervention-related major bleeding at 30 days	1468 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	RR 0.33 (0.19 to 0.55)	75 per 1000	50 fewer per 1000 (from 34 fewer to 61 fewer)
Need for reintervention (aortic reintervention) at 12 months	1468 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	OR 1.25 (0.34 to 4.64)	5 per 1000	1 more per 1000 (from 3 fewer to 18 more)
Length of stay (following initial intervention)	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgery replacement (unclear/mixed invasiveness)	Risk difference with transcatheter replacement (95% CI)
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	1468 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	RR 2.84 (2.06 to 3.93)	61 per 1000	112 more per 1000 (from 65 more to 179 more)
Intervention-related AF at 30 days	1468 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	RR 0.22 (0.17 to 0.29)	354 per 1000	276 fewer per 1000 (from 251 fewer to 294 fewer)
Major vascular complications at 30 days	1468 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.17 (0.68 to 1.99)	33 per 1000	6 more per 1000 (from 11 fewer to 33 more)
Prosthetic valve endocarditis at 12 months	1468 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	OR 0.67 (0.12 to 3.87)	4 per 1000	1 fewer per 1000 (from 4 fewer to 11 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment as invasiveness of surgery in surgery group is unclear
[c]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[d]MIDs used to assess imprecision were ±10.63

1.4.4.2 Aortic stenosis (bicuspid)

No evidence was identified for this stratum.

1.4.4.3 Aortic stenosis (mixed non-bicuspid and bicuspid or unclear)

Table 8: Clinical evidence summary: Minimally invasive surgery replacement vs. standard surgery replacement

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
All-cause mortality at 12 months	97 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.31 (0.31 to 5.53)	63 per 1000	20 more per 1000 (from 43 fewer to 285 more)
Cardiac mortality at 12 months	137 (2 studies)	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 1.59 (0.12 to 21.43)	50 per 1000	30 more per 1000 (from 80 fewer to 130 more)[d]
Intervention-related mortality at 30 days	354 (5 studies) 7-30 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.79 (0.30 to 2.08)	40 per 1000	10 fewer per 1000 (from 50 fewer to 30 more)[d]
Quality of life (EQ-5D) at 3 months Scale from: 0 to 1.	94 (1 study) 3 months	⨁⨁⊖⊖ VERY LOW[a,b,e] due to risk of bias, imprecision		The mean quality of life (eq-5d) at 3 months in the	The mean quality of life (EQ-5D) at 3 months in the intervention groups was 0 higher (0.04 lower to 0.04 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
				control groups was 0.9	
Quality of life (EQ-5D-5L index) at 12 months Scale from: -0.654 to 1.00.	94 (1 study) 12 months	⨁⨁⨀⨀ LOW[a,f] due to risk of bias		The mean quality of life (EQ-5D-5L index) at 12 months in the control groups was 0.90	The mean quality of life (EQ-5D-5L index) at 12 months in the intervention groups was 0.02 higher (0.03 lower to 0.07 higher)
Quality of life (EQ-5D-5L utilities - health index) at 12 months Scale from: 0 to 100.	94 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW[a,b,g] due to risk of bias, imprecision		The mean quality of life (EQ-5D-5L utilities - health index) at 12 months in the control groups was 92.9	The mean quality of life (EQ-5D-5L utilities - health index) at 12 months in the intervention groups was 1.60 higher (2.27 lower to 5.47 higher)
Quality of life (EQ-5D-5L utilities - severity index) at 12 months Scale from: 0 to 100.	94 (1 study) 12 months	⨁⨁⨀⨀ LOW[a,h] due to risk of bias		The mean quality of life (EQ-5D-5L utilities - severity index) at 12 months in the control groups was	The mean quality of life (EQ-5D-5L utilities - severity index) at 12 months in the intervention groups was 1.70 lower (5.57 lower to 2.17 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
				7.1	
Quality of life (EQ-5D-5L utilities - visual scale) at 12 months Scale from: 0 to 100.	94 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b, i] due to risk of bias, imprecision		The mean quality of life (EQ-5D-5L utilities - visual scale) at 12 months in the control groups was 80.43	The mean quality of life (EQ-5D-5L utilities - visual scale) at 12 months in the intervention groups was 1.08 lower (7.55 lower to 5.39 higher)
Onset or exacerbation of heart failure at ≥12 months	Not reported				
Intervention-related stroke or TIA at 30 days	234 (3 studies) 30 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.88 (0.41 to 8.58)	20 per 1000	20 more per 1000 (from 30 fewer to 60 more)[d]
Intervention-related major bleeding at 30 days	311 (4 studies) 72 h -30 days	⨁⊖⊖⊖ VERY LOW[a,b,j] due to risk of bias, indirectness imprecision	RR 0.85 (0.57 to 1.27)	66 per 1000	30 fewer per 1000 (from 110 fewer to 40 more)[d]
Need for re-intervention at 12 months	351 (5 studies) 7-30 days	⨁⊖⊖⊖ VERY LOW[a,b,k] due to risk of bias, indirectness, imprecision	RR 1.04 (0.40 to 2.69)	40 per 1000	0 more per 1000 (from 40 fewer to 40 more)[d]
Length of hospital stay (days)	217 (3 studies)	⨁⨁⨁⨁ HIGH[l]		The mean length of	The mean length of hospital stay (days) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
	in-hospital -30 days			hospital stay (days) ranged across control groups from 6.18-10.33 days	0.2 lower (0.65 lower to 0.25 higher)
Length of hospital stay (days)	40 (1 study) 30 days	⨁⨁⨁⊖ MODERATE[a] due to risk of bias		Median (IQR) 5 (5-6) days	Median 1 day higher
Length of intensive care unit stay (days)	100 (1 study) in-hospital	⨁⊖⊖⊖ VERY LOW[a,b,m] due to risk of bias, imprecision		The mean length of intensive care unit stay in the control groups was 5.06 days	The mean length of intensive care unit stay in the intervention groups was 1.41 days lower (3.48 lower to 0.66 higher)
Re-hospitalisation at ≥12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	234 (3 studies) unclear - 30 days	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.70 (0.11 to 4.66)	60 per 1000	10 fewer per 1000 (from 90 fewer to 60 more)[d]
New-onset atrial fibrillation at 30 days	180 (3 studies) postoperative - 30 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.99 (0.61 to 1.58)	286 per 1000	3 fewer per 1000 (from 112 fewer to 166 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
Intervention-related major vascular complications at 30 days	Not reported				
Prosthetic valve endocarditis at 12 months	188 (2 studies) 12 months	⨁⊖⊖⊖ VERY LOW[a,n] due to risk of bias, imprecision	RD 0 (-0.04 to 0.04)	11 per 1000	0 fewer per 1000 (from 40 fewer to 40 more)[o]

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c]Downgraded by 1 increment because of heterogeneity that cannot be explained by subgroup analysis.
[d]Absolute effect calculated manually using risk difference as zero events in one arm of some studies
[e]MIDs used to assess imprecision were ±0.03
[f]MIDs used to assess imprecision were ±0.075
[g]MIDs used to assess imprecision were ±1.03
[h]MIDs used to assess imprecision were ±6.00
[i]MIDs used to assess imprecision were ±7.21
[j]Downgraded by 1 increment as the study with the most weighting in the meta-analysis reports transfusion only and unclear whether captures all major bleeding events
[k]Downgraded because the outcome was reported at <3 months follow-up
[l]MIDs used to assess imprecision were ±1.20
[m]MIDs used to assess imprecision were ±3.425
[n]Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[o]Absolute effect calculated manually using risk difference as zero events in both arms of one of the studies

1.4.4.4 Aortic regurgitation (non-bicuspid)

No evidence was identified for this stratum.

1.4.4.5 Aortic regurgitation (bicuspid)

No evidence was identified for this stratum.

1.4.4.6 Aortic regurgitation (mixed non-bicuspid and bicuspid or unclear)

No evidence was identified for this stratum.

1.4.4.7 Mixed/unclear aortic valve disease

Table 9: Clinical evidence summary: Minimally invasive surgery replacement vs. standard surgery replacement

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional surgical replacement	Risk difference with Minimally invasive surgical replacement (95% CI)
All-cause mortality (time to event)	191 (2 studies) 12-30 months	⨁⊖⊖⊖ VERY LOW[b,c,d,e] due to risk of bias, inconsistency, indirectness, imprecision	HR 1.50 (0.61 to 3.71)	81 per 1000[a]	38 more per 1000 (from 31 fewer to 189 more)
All-cause mortality (dichotomous)	98 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[d,e] due to indirectness, imprecision	RR 1 (0.21 to 4.71)	61 per 1000	0 fewer per 1000 (from 48 fewer to 227 more)
Cardiac mortality at 12 months	329 (3 studies)	⨁⊖⊖⊖ VERY LOW[b,d,g] due to risk of bias,	RD 0.02 (-0.02 to 0.07)	35 per 1000	20 more per 1000 (from 20 fewer to 70 more)f

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional surgical replacement	Risk difference with Minimally invasive surgical replacement (95% CI)
	postoperative - 2 years	indirectness, imprecision			
Intervention-related mortality up to 30 days	542 (5 studies) <30 days/in-hospital/postoperative	⨁⊖⊖⊖ VERY LOW[b,d,g] due to risk of bias, indirectness, imprecision	RD 0.00 (-0.02 to 0.03)	19 per 1000	0 fewer per 1000 (from 20 fewer to 30 more)f
Quality of life (EQ-5D, final value) EQ-5D. Scale from: 0 to 1.	187 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[b,d,e,h] due to risk of bias, indirectness, imprecision		The mean quality of life (EQ-5D, final value) in the control groups was 0.78	The mean quality of life (EQ-5D, final value) in the intervention groups was 0.05 higher (0.03 lower to 0.13 higher)
Quality of life (SF-36 bodily pain, final value) SF-36 bodily pain subscale. Scale from: 0 to 100.	185 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[b,d,e,i] due to risk of bias, indirectness, imprecision		The mean quality of life (SF-36 bodily pain, final value) in the control groups was 72	The mean quality of life (SF-36 bodily pain, final value) in the intervention groups was 4 higher (5.11 lower to 13.11 higher)
Quality of life (SF-36 general health, final value) Scale from: 0 to 100.	186 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[b,d,e,j] due to risk of bias, indirectness, imprecision		The mean quality of life (SF-36 general health, final value) in the control groups was 62	The mean quality of life (SF-36 general health, final value) in the intervention groups was 6 higher (1.49 lower to 13.49 higher)
Quality of life (SF-36 mental health, final value) SF-36 mental health. Scale from: 0 to 100.	186 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[b,d,e,i] due to risk of bias, indirectness		The mean quality of life (SF-36 mental health, final value) in the control groups was 73	The mean quality of life (SF-36 mental health, final value) in the intervention groups was 3 higher (4.04 lower to 10.04 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional surgical replacement	Risk difference with Minimally invasive surgical replacement (95% CI)
Quality of life (SF-36 physical functioning, final value) SF-36 physical functioning. Scale from: 0 to 100.	186 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[b,d,e,i] due to risk of bias, indirectness, imprecision		The mean quality of life (SF-36 physical functioning, final value) in the control groups was 67	The mean quality of life (SF-36 physical functioning, final value) in the intervention groups was 7 higher (1.8 lower to 15.8 higher)
Quality of life (SF-36 role emotional, final value) SF-36 role emotional. Scale from: 0 to 100.	183 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[b,d,e,k] due to risk of bias, indirectness, imprecision		The mean quality of life (SF-36 role emotional, final value) in the control groups was 71	The mean quality of life (SF-36 role emotional, final value) in the intervention groups was 5 higher (6.8 lower to 16.8 higher)
Quality of life (SF-36 role physical, final value) SF-36 role physical. Scale from: 0 to 100.	183 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[b,d,e,i] due to risk of bias, indirectness, imprecision		The mean quality of life (SF-36 role physical, final value) in the control groups was 52	The mean quality of life (SF-36 role physical, final value) in the intervention groups was 12 higher (1.1 lower to 25.1 higher)
Quality of life (SF-36 social functioning, final value) SF-36 social functioning. Scale from: 0 to 100.	183 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[b,d,e,i] due to risk of bias, indirectness, imprecision		The mean quality of life (SF-36 social functioning, final value) in the control groups was 78	The mean quality of life (SF-36 social functioning, final value) in the intervention groups was 3 higher (5.72 lower to 11.72 higher)
Quality of life (SF-36 vitality, final value) SF-36 vitality. Scale from: 0 to 100.	186 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[b,d,e,k] due to risk of bias, indirectness, imprecision		The mean quality of life (SF-36 vitality, final value) in the control groups was 54	The mean quality of life (SF-36 vitality, final value) in the intervention groups was 6 higher (1.49 lower to 13.49 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional surgical replacement	Risk difference with Minimally invasive surgical replacement (95% CI)
Onset or exacerbation of heart failure at ≥12 months	Not reported				
Intervention-related stroke at 30 days	152 (2 studies) postoperative	⨁⊖⊖⊖ VERY LOW[b,d,g] due to risk of bias, indirectness, imprecision	RD 0 (-0.10 to 0.02)	39 per 1000	0 fewer per 1000 (from 100 fewer to 20 more)f
Intervention-related major bleeding (re-exploration for bleeding) at 30 days	332 (4 studies) <30 days/postoperative	⨁⊖⊖⊖ VERY LOW[b,d,e] due to risk of bias, indirectness, imprecision	RR 0.33 (0.12 to 0.95)	78 per 1000	50 fewer per 1000 (from 100 fewer to 10 more)[l]
Need for re-intervention at 12 months (30 months)	112 (1 study) 30 months	⨁⊖⊖⊖ VERY LOW[b,d,e] due to risk of bias, indirectness, imprecision	HR 0.87 (0.17 to 4.45)	54 per 1000[m]	7 fewer per 1000 (from 44 fewer to 164 more)
Need for re-intervention	180 (1 study) 30-354 days	⨁⊖⊖⊖ VERY LOW[b,d,e] due to risk of bias, indirectness, imprecision	RR 2.51 (0.52 to 12.1)	24 per 1000	36 more per 1000 (from 12 fewer to 266 more)
Length of hospital stay (final value) after intervention	634 (7 studies)	⨁⊖⊖⊖ VERY LOW[b,c,d,e,n] due to risk of bias, inconsistency, indirectness, imprecision		The mean length of hospital stay (final value) after intervention ranged across control groups from 8-17.9 days	The mean length of hospital stay (final value) after intervention in the intervention groups was 1.67 days lower (2.73 to 0.61 lower)
Length of intensive care unit stay (final value) after intervention	112	⨁⊖⊖⊖		The mean length of intensive care unit stay (final value)	The mean length of intensive care unit stay (final value)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional surgical replacement	Risk difference with Minimally invasive surgical replacement (95% CI)
	(1 study)	VERY LOW[b,d,o] due to risk of bias, indirectness		after intervention in the control groups was 1.7 days	after intervention in the intervention groups was 0.10 days lower (0.34 lower to 0.14 higher)
Re-hospitalisation	Not reported				
Intervention-related pacemaker implantation at 30 days	40 (1 study) postoperative Dogan 2003	⨁⊖⊖⊖ VERY LOW[b,d,e,p] due to risk of bias, indirectness, imprecision	OR 7.39 (0.15 to 372.38)	0 per 1000	50 more per 1000 (from 80 fewer to 180 more)[l]
	112 (1 study) operative Shneider 2020	⨁⊖⊖⊖ VERY LOW[b,d,e,p] due to risk of bias, indirectness, imprecision	OR 0.14 (0 to 6.82)	18 per 1000	20 fewer per 1000 (from 70 fewer to 30 more)[l]
Intervention-related atrial fibrillation and postoperative arrhythmias	140 (2 studies)	⨁⊖⊖⊖ VERY LOW[b,d,e,q] due to risk of bias, indirectness, imprecision	RR 0.71 (0.35 to 1.47)	221 per 1000	64 fewer per 1000 (from 144 fewer to 104 more)
Intervention-related major vascular complications at 30 days	Not reported				
Prosthetic valve endocarditis ≥12 months	Not reported				

[a]Control group risk taken from events in Nair 2018 study as number of events not clear in the other study
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c]Downgraded by 1 increment because of heterogeneity that cannot be explain by subgroup analysis
[d]Downgraded due to the type of aortic valve disease being poorly defined

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional surgical replacement	Risk difference with Minimally invasive surgical replacement (95% CI)

[e]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[f]Absolute effect calculated manually using risk difference as zero events in both arms of one study.
[g]Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[h]MIDs used to assess imprecision were ±0.03
[i]MIDs used to assess imprecision were ±3.00
[j]MIDs used to assess imprecision were ±2.00
[k]MIDs used to assess imprecision were ±4.00
[l]Absolute effect calculated manually using risk difference as zero events in one arm of at least one study
[m]Control group risk estimated from data in KM curves
[n]MIDs used to assess imprecision were ±1.15
[o]MIDs used to assess imprecision were ±0.35
[p]For this outcome, the point estimate of one study in opposite direction to the other study. Subgroup analyses could not be performed as only two studies. Studies therefore kept separate rather than pooling.
[q]Downgraded due to inclusion of other types of postoperative arrhythmias than atrial fibrillation

1.4.4.3 Mitral stenosis

Table 10: Clinical evidence summary: Minimally invasive surgery repair vs. standard surgery repair

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with minimally invasive surgery repair (95% CI)
All-cause mortality at 12 months	60 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RD 0 (-0.06 to 0.06)	0 per 1000	0 fewer per 1000 (from 60 fewer to 60 more)[a]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with minimally invasive surgery repair (95% CI)
Cardiac mortality at 12 months	60 (1 study) 7 years	⨁⨀⨀⨀ VERY LOW[b,c] due to risk of bias, imprecision	RD 0 (-0.06 to 0.06)	0 per 1000	0 fewer per 1000 (from 60 fewer to 60 more)[a]
Intervention-related mortality at 30 days	60 (1 study)	⨁⨀⨀⨀ VERY LOW[b,c] due to risk of bias, imprecision	RD 0 (-0.06 to 0.06)	0 per 1000	0 fewer per 1000 (from 60 fewer to 60 more)[a]
Health-related quality of life at 12 months	Not reported				
Onset or exacerbation of heart failure at 12 months	Not reported				
Intervention-related stroke or TIA at 30 days	60 (1 study)	⨁⨀⨀⨀ VERY LOW[b,c] due to risk of bias, imprecision	RD 0 (-0.06 to 0.06)	0 per 1000	0 fewer per 1000 (from 60 fewer to 60 more)[a]
Intervention-related major bleeding at 30 days	Not reported				
Need for reintervention at 12 months	60 (1 study) 7 years	⨁⨁⨁⨀ MODERATE[b] due to risk of bias	RR 7.5 (1.88 to 29.99)	67 per 1000	436 more per 1000 (from 59 more to 1000 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with minimally invasive surgery repair (95% CI)
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	Not reported				
Intervention-related atrial fibrillation at 30 days	Not reported				
Intervention-related major vascular complications at 30 days	Not reported				
Prosthetic valve endocarditis at 12 months	Not reported				

[a]Absolute effect calculated manually using risk difference as zero events in both arms of the study
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with minimally invasive surgery repair (95% CI)
at very high risk of bias [c]Imprecision assessed using sample size as zero events in both arms of the study. Very serious imprecision as sample size <70.					

Table 11: Clinical evidence summary: Transcatheter repair vs. standard surgery repair

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with transcatheter repair (95% CI)
All-cause mortality at 12 months	120 (2 studies) 3-7 years	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RD 0.02 (-0.04 to 0.07)	0 per 1000	20 more per 1000 (from 40 fewer to 70 more)[a]
Cardiac mortality at 12 months	120 (2 studies) 3-7 years	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RD 0.02 (-0.04 to 0.07)	0 per 1000	20 more per 1000 (from 40 fewer to 70 more)[a]
Intervention-related mortality at 30 days	120 (2 studies)	⨁⊖⊖⊖ VERY LOW[b,c,e] due to risk of bias, indirectness, imprecision	RD 0 (-0.05 to 0.05)	0 per 1000	0 fewer per 1000 (from 50 fewer to 50 more)[a]
Health-related quality of life at 12 months	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with transcatheter repair (95% CI)
Onset or exacerbation of heart failure at 12 months	Not reported				
Intervention-related stroke or TIA at 30 days	120 (2 studies)	⨁⊖⊖⊖ VERY LOW[b,c,e] due to risk of bias, indirectness, imprecision	RD 0 (-0.05 to 0.05)	0 per 1000	0 fewer per 1000 (from 50 fewer to 50 more)[a]
Intervention-related major bleeding at 30 days	Not reported				
Need for reintervention at 12 months	60 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[b,f] due to risk of bias, imprecision	RR 1.5 (0.27 to 8.34)	67 per 1000	34 more per 1000 (from 49 fewer to 492 more)
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at 12 months	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with transcatheter repair (95% CI)
Intervention-related pacemaker implantation at 30 days	Not reported				
Intervention-related major vascular complications at 30 days	Not reported				
Intervention-related atrial fibrillation at 30 days	60 (1 study)	⨁⊖⊖⊖ VERY LOW[b,c,g] due to risk of bias, indirectness, imprecision	RD 0 (-0.06 to 0.06)	0 per 1000	0 fewer per 1000 (from 60 fewer to 60 more)[a]
Prosthetic valve endocarditis at 12 months	Not reported				

[a]Absolute effect calculated manually using risk difference as zero events in both arms of one or more studies
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c]Downgraded by 1 increment as some patients in one of the studies <18 years old - proportion unclear
[d]Downgraded by 2 increments as imprecision very serious based on OIS calculation
[e]Imprecision assessed using sample size as zero events in both arms of both studies. Serious imprecision as sample size >70 and <350
[f]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[g]Imprecision assessed using sample size as zero events in both arms of the study. Very serious imprecision as sample size <70

1 **Table 12: Clinical evidence summary: Transcatheter repair vs. minimally invasive surgery repair**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with minimally invasive surgery repair	Risk difference with transcatheter repair (95% CI)
All-cause mortality at 12 months	591 (5 studies) unclear-8 years	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RD 0 (-0.02 to 0.02)	0 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)[a]
Cardiac mortality at 12 months	591 (5 studies) unclear-8 years	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RD 0 (-0.02 to 0.02)	0 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)[a]
Intervention-related mortality at 30 days	594 (5 studies)	⨁⊖⊖⊖ VERY LOW[b,d,e] due to risk of bias, indirectness, imprecision	RD 0 (-0.02 to 0.02)	0 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)[a]
Health-related quality of life at 12 months	Not reported				
Onset or exacerbation of heart failure at 12 months	Not reported				
Intervention-related stroke or TIA at 30 days	590 (5 studies)	⨁⊖⊖⊖ VERY LOW[b,d,f] due to risk of bias, indirectness, imprecision	RD 0 (-0.01 to 0.02)	0 per 1000	0 fewer per 1000 (from 10 fewer to 20 more)[a]
Intervention-related major bleeding at 30 days	236 (2 studies)	⨁⊖⊖⊖ VERY LOW[b,d] due to risk of bias, imprecision	RD 0 (-0.02 to 0.04)	0 per 1000	10 more per 1000 (from 20 fewer to 40 more)[a]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with minimally invasive surgery repair	Risk difference with transcatheter repair (95% CI)
Need for reintervention at 12 months	391 (4 studies) unclear-8 years	⨁⊖⊖⊖ VERY LOW[b,g,h] due to risk of bias, inconsistency, imprecision	RR 1.13 (0.21 to 6.03)	12 per 1000	20 fewer per 1000 (from 200 fewer to 150 more)[a]
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	Not reported				
Intervention-related atrial fibrillation at 30 days	Not reported				
Prosthetic valve endocarditis at 12 months	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with minimally invasive surgery repair	Risk difference with transcatheter repair (95% CI)
Major vascular complications at 30 days	240 (2 studies)	⨁⨁⨀⨀ LOW[b] due to risk of bias	OR 8.02 (2.4 to 26.8)	0 per 1000	90 more per 1000 (from 40 more to 150 more)[a]

[a]Absolute effect calculated manually using risk difference as zero events in one or both arms of one or more studies
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c]Downgraded by 1 increment as two studies include some under 18 years old - proportion unclear. One study follow-up <3 months
[d]Downgraded by 2 increments as imprecision very serious based on OIS calculation
[e]Downgraded by 1 increment as two studies include some under 18 years old - proportion unclear.
[f]Downgraded by 1 increment as two studies include some under 18 years old - proportion unclear. Also one study reports hemiplegia rather than stroke specifically.
[g]Downgraded by 1 increment as heterogeneity is present but could not be explained by subgrouping strategies
[h]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 13: Clinical evidence summary: Transcatheter repair vs. surgical repair (unclear/mixed invasiveness)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgical repair (unclear/mixed invasiveness)	Risk difference with transcatheter repair (95% CI)
All-cause mortality at 12 months	80 (1 study) 2 years	⨁⨀⨀⨀ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RD 0 (-0.05 to 0.05)	0 per 1000	0 fewer per 1000 (from 50 fewer to 50 more)[a]
Cardiac mortality at 12 months	80 (1 study) 2 years	⨁⨀⨀⨀ VERY LOW[b,c,d] due to risk of bias,	RD 0 (-0.05 to 0.05)	0 per 1000	0 fewer per 1000 (from 50 fewer to 50 more)[a]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgical repair (unclear/mixed invasiveness)	Risk difference with transcatheter repair (95% CI)
		indirectness, imprecision			
Intervention-related mortality at 30 days	80 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RD 0 (-0.05 to 0.05)	0 per 1000	0 fewer per 1000 (from 50 fewer to 50 more)[a]
Health-related quality of life at 12 months	Not reported				
Onset or exacerbation of heart failure at 12 months	Not reported				
Intervention-related stroke or TIA at 30 days	Not reported				
Intervention-related major bleeding at 30 days	80 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[b,e] due to risk of bias, indirectness	OR 0.12 (0.02 to 0.74)	103 per 1000	130 fewer per 1000 (from 230 fewer to 20 fewer)[a]
Need for reintervention at 12 months	80 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RD 0 (-0.05 to 0.05)	0 per 1000	0 fewer per 1000 (from 50 fewer to 50 more)[a]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgical repair (unclear/mixed invasiveness)	Risk difference with transcatheter repair (95% CI)
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	80 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[b,f,g] due to risk of bias, indirectness, imprecision	OR 0.13 (0.01 to 2.15)	52 per 1000	50 fewer per 1000 (from 130 fewer to 30 more)[a]
Intervention-related atrial fibrillation at 30 days	80 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[b,f] due to risk of bias, indirectness	OR 0.12 (0.02 to 0.62)	102 per 1000	150 fewer per 1000 (from 270 fewer to 30 fewer)[a]
Major vascular complications at 30 days	80 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[b,f,g] due to risk of bias, indirectness, imprecision	OR 7.58 (0.47 to 123.37)	0 per 1000	50 more per 1000 (from 30 fewer to 130 more)[a]
Prosthetic valve endocarditis at 12 months	Not reported				

[a]Absolute effect calculated manually using risk difference as zero events in at least one arm of one or more studies
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgical repair (unclear/mixed invasiveness)	Risk difference with transcatheter repair (95% CI)
at very high risk of bias [c]Downgraded by 1 increment as some patients were <18 years old - proportion unclear [d]Imprecision assessed using sample size as zero events in both arms of the study. Serious imprecision as sample size >70 and <350 [e]Downgraded by 1 increment as some patients in the study were <18 years old - proportion unclear. Also time-point measured at for this outcome unclear and unclear whether all were major bleeding events [f]Downgraded by 1 increment as some patients in the study were <18 years old - proportion unclear. Also time-point measured at for this outcome unclear. [g]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

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1.4.42 Mitral regurgitation

3 **Table 14: Clinical evidence summary: Evidence not suitable for GRADE analysis**

Study	Intervention and comparator	Outcome	Intervention results	Intervention group (n)	Comparator results	Comparator group (n)	Risk of bias
Medved 2010 [247]	Standard surgery replacement vs. standard surgery repair	Length of hospital stay post-intervention	Mean: 13.5 days	40	Mean:15 days	40	High

4

1 **Table 15: Clinical evidence summary: Standard surgery replacement vs. standard surgery repair**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with standard surgery replacement (95% CI)
All-cause mortality at 12 months	Not reported				
Cardiac mortality at 12 months	80 (1 study) in-hospital	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.5 (0.05 to 5.3)	50 per 1000	25 fewer per 1000 (from 47 fewer to 215 more)
Intervention-related mortality at 30 days	80 (1 study) in-hospital	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.5 (0.05 to 5.3)	50 per 1000	25 fewer per 1000 (from 47 fewer to 215 more)
Health-related quality of life at 12 months	Not reported				
Onset or exacerbation of heart failure at 12 months	Not reported				
Intervention-related stroke or TIA at 30 days	80 (1 study) in-hospital	⨁⊖⊖⊖ VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 1 (0.06 to 15.44)	25 per 1000	0 fewer per 1000 (from 24 fewer to 361 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with standard surgery replacement (95% CI)
Intervention-related major bleeding at 30 days	Not reported				
Need for reintervention at 12 months	80 (1 study) in-hospital	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.33 (0.04 to 3.07)	75 per 1000	50 fewer per 1000 (from 72 fewer to 155 more)
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	Not reported				
Intervention-related atrial fibrillation at 30 days	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with standard surgery replacement (95% CI)
Intervention-related major vascular complications at 30 days	Not reported				
Prosthetic valve endocarditis at 12 months	Not reported				

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded for indirectness as follow-up was <3 months
[c]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[d]Downgraded for indirectness as neurological dysfunction could include events other than stroke and TIA

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2 **Table 16: Clinical evidence summary: Minimally invasive surgery repair vs. standard surgery repair**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with minimally invasive surgery repair (95% CI)
All-cause mortality at 12 months	159 (1 study) 3 years	⨁⨁⨀⨀ LOW[a] due to imprecision	RR 1.01 (0.21 to 4.87)	38 per 1000	0 more per 1000 (from 30 fewer to 147 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with minimally invasive surgery repair (95% CI)
Cardiac mortality at 12 months	Not reported				
Intervention-related mortality at 30 days	160 (1 study) intraoperative/early postoperative	⨁⨁⨀⨀ LOW[a] due to imprecision	RR 1 (0.14 to 6.93)	25 per 1000	0 fewer per 1000 (from 22 fewer to 148 more)
Quality of life at 12 months (SF-36 general health domain) Scale from: 0 to 100.	153 (1 study) 3 years	⨁⨁⨁⨀ LOW[a,b,c] due to risk of bias, imprecision		The mean quality of life at 12 months (sf-36 general health domain) in the control groups was 84.2	The mean quality of life at 12 months (SF-36 general health domain) in the intervention groups was 1.3 lower (4.22 lower to 1.62 higher)
Quality of life at 12 months (SF-36 mental health domain) Scale from: 0 to 100.	153 (1 study) 3 years	⨁⨁⨁⨀ LOW[a,b,d] due to risk of bias, imprecision		The mean quality of life at 12 months (SF-36 mental health domain) in the control groups was 81.5	The mean quality of life at 12 months (SF-36 mental health domain) in the intervention groups was 0.9 higher (1.99 lower to 3.79 higher)
Quality of life at 12 months (SF-36 physical activity domain) Scale from: 0 to 100.	153 (1 study) 3 years	⨁⨁⨁⨀ LOW[a,b,d] due to risk of bias, imprecision		The mean quality of life at 12 months (SF-36 physical activity domain) in the control groups was 79.7	The mean quality of life at 12 months (SF-36 physical activity domain) in the intervention groups was 0.6 lower (3.41 lower to 2.21 higher)
Quality of life at 12 months (SF-36 role limitation domain) Scale from: 0 to 100.	153 (1 study) 3 years	⨁⨁⨁⨀ LOW[a,b,d] due to risk of bias, imprecision		The mean quality of life at 12 months (SF-36 role limitation domain) in the control groups was 79.5	The mean quality of life at 12 months (SF-36 role limitation domain) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with minimally invasive surgery repair (95% CI)
					1 lower (4.05 lower to 2.05 higher)
Quality of life at 12 months (SF-36 social activities domain) Scale from: 0 to 100.	153 (1 study) 3 years	⨁⨁⨁⊖ MODERATE[b,d] due to risk of bias		The mean quality of life at 12 months (SF-36 social activities domain) in the control groups was 83.8	The mean quality of life at 12 months (SF-36 social activities domain) in the intervention groups was 0.4 higher (1.82 lower to 2.62 higher)
Quality of life at 12 months (SF-36 vitality domain) Scale from: 0 to 100.	153 (1 study) 3 years	⨁⨁⨁⊖ LOW[a,b,c] due to risk of bias, imprecision		The mean quality of life at 12 months (SF-36 vitality domain) in the control groups was 78.8	The mean quality of life at 12 months (SF-36 vitality domain) in the intervention groups was 1 higher (1.66 lower to 3.66 higher)
Onset or exacerbation of heart failure at 12 months	Not reported				
Intervention-related stroke or TIA at 30 days	140 (1 study) intraoperative/early postoperative	⨁⊖⊖⊖ VERY LOW[a,e] due to indirectness, imprecision	RR 0.5 (0.05 to 5.39)	29 per 1000	15 fewer per 1000 (from 28 fewer to 127 more)
Intervention-related major bleeding at 30 days	140 (1 study) intraoperative/early postoperative	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 1.33 (0.31 to 5.74)	43 per 1000	14 more per 1000 (from 30 fewer to 204 more)
Need for reintervention at 12 months	153 (1 study) 3 years	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 2.03 (0.19 to 21.88)	13 per 1000	13 more per 1000 (from 11 fewer to 271 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with minimally invasive surgery repair (95% CI)
Length of hospital stay post-intervention	160 (1 study)	⨁⨁⨁⊖ MODERATE[a,f] due to imprecision		The mean length of hospital stay post-intervention in the control groups was 11.6 days	The mean length of hospital stay post-intervention in the intervention groups was 3.1 days lower (4.57 to 1.63 lower)
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	Not reported				
Intervention-related atrial fibrillation at 30 days	Not reported				
Intervention-related major vascular complications at 30 days	Not reported				
Prosthetic valve endocarditis at 12 months	153 (1 study) 3 years	⨁⊖⊖⊖ VERY LOW[b,i,j] due to risk of bias, indirectness, imprecision	RD 0 (-0.03 to 0.03)[h]	0 per 1000	0 fewer per 1000 (from 30 fewer to 30 more)[g]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery repair	Risk difference with minimally invasive surgery repair (95% CI)

[a]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c]MIDs used to assess imprecision were ±2.00
[d]MIDs used to assess imprecision were ±3.00
[e]Downgraded as neurological complications may include events other than stroke and TIA
[f]MIDs used to assess imprecision were ±2.50
[g]Absolute effect calculated manually using risk difference as zero events in both arms.
[h]Presented as risk difference
[i]Downgraded as outcome may not be prosthetic valve endocarditis as specified in the protocol based on the interventions being repair rather than replacement procedures
[j]Imprecision assessed using sample size as zero events in both arms - serious imprecision as sample size is >70 and <350

Table 17: Clinical evidence summary: Minimally invasive surgery (mixed repair/replacement) vs. standard surgery (mixed repair/replacement)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery (mixture of repair and replacement)	Risk difference with minimally invasive surgery (mixture of repair and replacement) (95% CI)
All-cause mortality at 12 months	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery (mixture of repair and replacement)	Risk difference with minimally invasive surgery (mixture of repair and replacement) (95% CI)
Cardiac mortality at 12 months	40 (1 study) in-hospital	⨁⊖⊖⊖ VERY LOW[c,d,e] due to risk of bias, indirectness, imprecision	RD 0 (-0.09 to 0.09)[b]	0 per 1000	0 fewer per 1000 (from 90 fewer to 90 more)[a]
Intervention-related mortality at 30 days	40 (1 study) in-hospital	⨁⊖⊖⊖ VERY LOW[c,e,f] due to risk of bias, indirectness, imprecision	RD 0 (-0.09 to 0.09)[b]	0 per 1000	0 fewer per 1000 (from 90 fewer to 90 more)[a]
Health-related quality of life at 12 months	Not reported				
Onset or exacerbation of heart failure at 12 months	40 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[c,d,g] due to risk of bias, indirectness, imprecision	RR 1 (0.07 to 14.9)	50 per 1000	0 fewer per 1000 (from 47 fewer to 695 more)
Intervention-related stroke or TIA at 30 days	40 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[c,g] due to risk of bias, imprecision	RR 1 (0.07 to 14.9)	50 per 1000	0 fewer per 1000 (from 47 fewer to 695 more)
Intervention-related major bleeding at 30 days	40 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[c,e,f] due to risk of bias, indirectness, imprecision	OR 0.14 (0 to 6.82)	50 per 1000	50 fewer per 1000 (from 180 fewer to 80 more)[h]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery (mixture of repair and replacement)	Risk difference with minimally invasive surgery (mixture of repair and replacement) (95% CI)
Need for reintervention at 12 months	Not reported				
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	40 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[c,f,g] due to risk of bias, indirectness, imprecision	OR 0.14 (0 to 6.82)	50 per 1000	50 fewer per 1000 (from 180 fewer to 80 more)[h]
Intervention-related atrial fibrillation at 30 days	Not reported				
Intervention-related major vascular complications at 30 days	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery (mixture of repair and replacement)	Risk difference with minimally invasive surgery (mixture of repair and replacement) (95% CI)
Prosthetic valve endocarditis at 12 months	Not reported				

[a]Absolute effect calculated manually using risk difference as zero events in both arms of the study
[b]Presented as risk difference
[c]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[d]Downgraded 2 increments as indirect population and interventions: proportion with mitral stenosis rather than mitral regurgitation and mixture of repair and replacement interventions within each study arm. In addition, follow-up <3 months.
[e]Imprecision assessed using sample size as zero events in both arms of the study. Very serious imprecision as sample size <70.
[f]Downgraded 2 increments as indirect population and interventions: proportion with mitral stenosis rather than mitral regurgitation and mixture of repair and replacement interventions within each study arm.
[g]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[h]Absolute effect calculated manually using risk difference as zero events in one arm of the study

Table 18: Clinical evidence summary: Surgical replacement (unclear/mixed invasiveness) vs. surgical repair (unclear/mixed invasiveness)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgical repair (unclear/mixed invasiveness)	Risk difference with surgical replacement (unclear/mixed invasiveness) (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgical repair (unclear/mixed invasiveness)	Risk difference with surgical replacement (unclear/mixed invasiveness) (95% CI)
All-cause mortality at 12 months (time to event, 24 months) - HR	339 (2 studies) 2 years	⨁⊖⊖⊖ VERY LOW[a,b,c,d] due to risk of bias, inconsistency, indirectness, imprecision	HR 1.95 (0.64 to 5.94)	118 per 1000	99 more per 1000 (from 41 fewer to 407 more)
Cardiac mortality at 12 months	88 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 6.98 (0.91 to 53.47)	24 per 1000	144 more per 1000 (from 2 fewer to 1000 more)
Intervention-related mortality at 30 days	339 (2 studies)	⨁⊖⊖⊖ VERY LOW [a,b,c] due to risk of bias, indirectness, imprecision	RR 2.54 (0.6 to 10.77)	8 per 1000	20 more per 1000 (from 1 fewer to 60 more)[e]
Quality of life at 12 months (EQ-5D) Scale from: 0 to 100.	171 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW [a,b,f] due to risk of bias, indirectness		The mean quality of life at 12 months (EQ-5D) in the control groups was 73.7	The mean quality of life at 12 months (EQ-5D) in the intervention groups was 0.2 higher (5.33 lower to 5.73 higher)
Quality of life at 12 months (MLWHF questionnaire) Scale from: 0 to 105.	180 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW [a,b,c,g] due to risk of bias, indirectness, imprecision		The mean quality of life at 12 months (MLWHF questionnaire) in the control groups was 24.5	The mean quality of life at 12 months (MLWHF questionnaire) in the intervention groups was 4.9 lower (11.11 lower to 1.31 higher)
Quality of life at 12 months (SF-12 mental function) Scale from: 0 to 100.	178 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW [a,b,h] due to risk of bias, indirectness		The mean quality of life at 12 months (SF-12 mental function) in the control groups was 46.8	The mean quality of life at 12 months (SF-12 mental function) in the intervention groups was 0.1 higher (1.88 lower to 2.08 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgical repair (unclear/mixed invasiveness)	Risk difference with surgical replacement (unclear/mixed invasiveness) (95% CI)
Quality of life at 12 months (SF-12 physical function) Scale from: 0 to 100.	178 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW [a,b,i] due to risk of bias, indirectness		The mean quality of life at 12 months (SF-12 physical function) in the control groups was 43.6	The mean quality of life at 12 months (SF-12 physical function) in the intervention groups was 0.6 higher (1.63 lower to 2.83 higher)
Onset or exacerbation of heart failure at 12 months	169 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW [a,b,c] due to risk of bias, indirectness, imprecision	RR 1.01 (0.3 to 3.37)	59 per 1000	1 more per 1000 (from 41 fewer to 140 more)
Intervention-related stroke or TIA at 30 days	339 (2 studies)	⨁⊖⊖⊖ VERY LOW [a,b,c] due to risk of bias, indirectness, imprecision	RR 1.54 (0.41 to 5.81)	12 per 1000	10 more per 1000 (from 20 fewer to 50 more)[e]
Intervention-related major bleeding at 30 days	88 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW [a,b,c] due to risk of bias, indirectness, imprecision	OR 6.5 (0.13 to 330.77)	0 per 1000	20 more per 1000 (from 40 fewer to 80 more)[e]
Need for reintervention at 12 months (24 months)	339 (2 studies) 2 years	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, indirectness	OR 0.17 (0.06 to 0.49)	74 per 1000	70 fewer per 1000 (from 30 fewer to 110 fewer)[e]
Length of stay post-intervention	251 (1 study)	⨁⨁⊖⊖ LOW [a,b,j] due to risk of bias, indirectness		The mean length of stay post-intervention in the control groups was 11.5 days	The mean length of stay post-intervention in the intervention groups was 0.4 days higher (1.78 lower to 2.58 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgical repair (unclear/mixed invasiveness)	Risk difference with surgical replacement (unclear/mixed invasiveness) (95% CI)
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	88 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW [a,b,c] due to risk of bias, indirectness, imprecision	RR 1.31 (0.23 to 7.45)	49 per 1000	15 more per 1000 (from 38 fewer to 316 more)
Major vascular complications at 30 days	88 (1 study) intraoperative	⨁⊖⊖⊖ VERY LOW [a,b,c] due to risk of bias, indirectness, imprecision	RR 0.87 (0.06 to 13.51)	24 per 1000	3 fewer per 1000 (from 23 fewer to 300 more)
Prosthetic valve endocarditis at 12 months	251 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW [a,b,c] due to risk of bias, indirectness, imprecision	OR 7.51 (0.47 to 120.72)	0 per 1000	20 more per 1000 (from 10 fewer to 40 more)[e]

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment as the interventions are indirect due to there being a mixture of minimally invasive and standard surgery replacement
[c]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[d]Downgraded by 1 increment because heterogeneity is present and subgrouping strategies cannot be used due to there being only two studies in the meta-analysis: I2=62%, p=0.10.
[e]Absolute effect calculated manually using risk difference as zero events in one arm of one of the studies
[f]MIDs used to assess imprecision were ±11.98
[g]MIDs used to assess imprecision were ±5.00
[h]MIDs used to assess imprecision were ±4.20

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgical repair (unclear/mixed invasiveness)	Risk difference with surgical replacement (unclear/mixed invasiveness) (95% CI)
[i]MIDs used to assess imprecision were ±3.83 [j]MIDs used to assess imprecision were ±4.50					

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3 **Table 19: Clinical evidence summary: Transcatheter repair vs. pharmacological management**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with pharmacological management	Risk difference with transcatheter repair (95% CI)
All-cause mortality at 12 months (time-to-event) - HR	918 (2 studies) 24 months	⨁⊖⊖⊖ VERY LOW [a,b,c] due to risk of bias, inconsistency, imprecision	HR 0.78 (0.48 to 1.28)	373 per 1000	68 fewer per 1000 (from 172 fewer to 77 more)
All-cause mortality at 12 months (dichotomous)	110 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW [a,c] due to risk of bias, imprecision	RR 0.79 (0.3 to 2.07)	172 per 1000	36 fewer per 1000 (from 120 fewer to 184 more)
Cardiac mortality at 12 months (time-to-event) - HR	918 (2 studies) 24 months	⨁⊖⊖⊖ VERY LOW [a,b,c] due to risk of bias, inconsistency, imprecision	HR 0.75 (0.45 to 1.25)	313 per 1000	68 fewer per 1000 (from 158 fewer to 62 more)
Intervention-related mortality at 30 days	424 (2 studies) 30 days	⨁⨁⊖⊖ LOW[c] due to imprecision	RR 1.35 (0.41 to 4.45)	22 per 1000	10 more per 1000 (from 20 fewer to 40 more)[d]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with pharmacological management	Risk difference with transcatheter repair (95% CI)
Quality of life at 12 months (EQ-5D) Scale from: 0 to 100.	180 (1 study) 12 months	⨁⨁⨀⨀ LOW [a,e] due to risk of bias		The mean quality of life at 12 months (EQ-5D) in the control groups was 58.6	The mean quality of life at 12 months (EQ-5D) in the intervention groups was 2.2 higher (3.43 lower to 7.83 higher)
Quality of life at 12 months (KCCQ overall) Scale from: 0 to 100.	312 (2 studies) 12-24 months	⨁⨀⨀⨀ VERY LOW [a,c,f] due to risk of bias, imprecision		The mean quality of life at 12 months (KCCQ overall) in the control groups was 7.63 for change scores (n=1) and 61.2 for final values (n=1)	The mean quality of life at 12 months (KCCQ overall) in the intervention groups was 7.13 higher (1.79 to 12.46 higher)
Quality of life at 12 months (SF-36 mental component) Scale from: 0 to 100.	217 (1 study) 24 months	⨁⨁⨀⨀ VERY LOW [a,c,g] due to risk of bias, imprecision		The mean quality of life at 12 months (SF-36 mental component) in the control groups was 48.9	The mean quality of life at 12 months (SF-36 mental component) in the intervention groups was 1.2 higher (2.06 lower to 4.46 higher)
Quality of life at 12 months (SF-36 physical component) Scale from: 0 to 100.	217 (1 study) 24 months	⨁⨀⨀⨀ VERY LOW [a,c,h] due to risk of bias, imprecision		The mean quality of life at 12 months (SF-36 physical component) in the control groups was 34.1	The mean quality of life at 12 months (SF-36 physical component) in the intervention groups was 4 higher (1.25 to 6.75 higher)
Onset of exacerbation of heart failure at 12 months	1038 (3 studies) 12-24 months	⨁⨀⨀⨀ VERY LOW [a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.77 (0.57 to 1.03)	515 per 1000	118 fewer per 1000 (from 221 fewer to 15 more)
Intervention-related stroke or TIA at 30 days	910 (2 studies) periprocedural-30 days	⨁⨀⨀⨀ VERY LOW [a,c,k] due to risk of bias, indirectness, imprecision	OR 7.76 (1.09 to 55.28)	0 per 1000	10 more per 1000 (from 0 more to 20 more)[i]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with pharmacological management	Risk difference with transcatheter repair (95% CI)
Intervention-related major bleeding at 30 days	304 (1 study) periprocedural	⨁⨁⨀⨀ LOW [c] due to imprecision	RR 1.83 (0.7 to 4.83)	39 per 1000	32 more per 1000 (from 12 fewer to 149 more)
Need for reintervention at 12 months (time-to-event) - HR	614 (1 study) 24 months	⨁⨀⨀⨀ VERY LOW [a,c] due to risk of bias, imprecision	HR 0.61 (0.27 to 1.38)	48 per 1000	18 fewer per 1000 (from 35 fewer to 18 more)
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at 12 months (time-to-event) - HR	614 (1 study) 24 months	⨁⨁⨀⨀ LOW [a,c] due to risk of bias, imprecision	HR 0.77 (0.64 to 0.93)	731 per 1000	95 fewer per 1000 (from 26 fewer to 163 fewer)
Rehospitalisation (for HF) at 12 months (dichotomous)	120 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW [a,c] due to risk of bias, imprecision	RR 0.76 (0.43 to 1.34)	364 per 1000	87 fewer per 1000 (from 207 fewer to 124 more)
Intervention-related pacemaker implantation at 30 days	Not reported				
Intervention-related atrial fibrillation at 30 days	Not reported				
Major vascular complications at 30 days	296 (1 study) periprocedural	⨁⨁⨁⨀ MODERATE [a] due to risk of bias	OR 8.04 (1.37 to 46.97)	0 per 1000	30 more per 1000 (from 0 more to 70 more) [d]
Prosthetic valve endocarditis at 12 months	120 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW [a,c] due to risk of bias, imprecision	OR 4.02 (0.18 to 90.74)	0 per 1000	20 more per 1000 (from 30 fewer to 80 more) [d]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with pharmacological management	Risk difference with transcatheter repair (95% CI)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b]Downgraded by 1 increment because heterogeneity is present and subgrouping strategies cannot be used due to the number of studies.

[c]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[d]Absolute effect calculated manually using risk difference as zero events in one arm of one study

[e]MIDs used to assess imprecision were ±8.95

[f]MIDs used to assess imprecision were ±11.53

[g]MIDs used to assess imprecision were ±3.00

[h]MIDs used to assess imprecision were ±2.00

[i]Absolute effect calculated manually using risk difference as zero events in one arm of both studies

[j]Downgraded by 1 increment as gas embolism included in events for one study

Table 20: Clinical evidence summary: Transcatheter repair vs. surgery (mixed repair/replacement and unclear/mixed invasiveness)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgery (mixed repair/replacement and mixed/unclear invasiveness)	Risk difference with transcatheter repair (95% CI)
All-cause mortality at 12 months	210 (1 study) 5 years	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.78 (0.46 to 1.32)	268 per 1000	59 fewer per 1000 (from 145 fewer to 86 more)
Cardiac mortality at 12 months	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgery (mixed repair/replacement and mixed/unclear invasiveness)	Risk difference with transcatheter repair (95% CI)
Intervention-related mortality at 30 days	274 (1 study)	⨁⊖⊖⊖ VERY LOW[b,c] due to indirectness, imprecision	RR 0.52 (0.07 to 3.65)	21 per 1000	10 fewer per 1000 (from 20 fewer to 56 more)
Quality of life at 12 months (SF-36 mental component)	193 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,c,d] due to risk of bias, indirectness, imprecision		The mean quality of life at 12 months (SF-36 mental component) in the control groups was 3.8	The mean quality of life at 12 months (SF-36 mental component) in the intervention groups was 1.9 higher (1.2 lower to 5 higher)
Quality of life at 12 months (SF-36 physical component)	192 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,c,e] due to risk of bias, indirectness, imprecision		The mean quality of life at 12 months (SF-36 physical component) in the control groups was 4.4	The mean quality of life at 12 months (SF-36 physical component) in the intervention groups was 0 higher (3.12 lower to 3.12 higher)
Onset or exacerbation of heart failure at 12 months	Not reported				
Intervention-related stroke or TIA at 30 days	274 (1 study)	⨁⊖⊖⊖ VERY LOW[b,c] due to indirectness, imprecision	RR 0.52 (0.07 to 3.65)	21 per 1000	10 fewer per 1000 (from 20 fewer to 56 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgery (mixed repair/replacement and mixed/unclear invasiveness)	Risk difference with transcatheter repair (95% CI)
Intervention-related major bleeding at 30 days	Not reported				
Need for reintervention at 12 months	210 (1 study) 5 years	⨁⨁⊖⊖ LOW[a,b] due to risk of bias, indirectness	RR 3.13 (1.3 to 7.5)	89 per 1000	190 more per 1000 (from 27 more to 578 more)
Length of stay (following initial intervention)	Not reported				
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	Note reported				
Intervention-related atrial fibrillation at 30 days	274 (1 study)	⨁⊖⊖⊖ VERY LOW[b,c] due to indirectness, imprecision	OR 4.61 (0.25 to 85.84)	0 per 1000	10 more per 1000 (from 10 fewer to 30 more)[f]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with surgery (mixed repair/replacement and mixed/unclear invasiveness)	Risk difference with transcatheter repair (95% CI)
Major vascular complications at 30 days	274 (1 study)	⨁⊖⊖⊖ VERY LOW[c,g] due to indirectness, imprecision	RR 0.52 (0.13 to 2.04)	43 per 1000	21 fewer per 1000 (from 37 fewer to 45 more)
Prosthetic valve endocarditis at 12 months	Not reported				

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded 1 increment as the surgical arm was a mixture of repair/replacement procedures and unclear/mixed invasiveness of surgery
[c]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[d]MIDs used to assess imprecision were ±3.00
[e]MIDs used to assess imprecision were ±2.00
[f]Absolute effect calculated manually using risk difference as zero events in one arm of the study
[g]Downgraded 2 increments as the surgical arm was a mixture of repair/replacement procedures and unclear/mixed invasiveness of surgery, and it was unclear whether events were all a result of vascular complications

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1.4.4.10 Unclear/mixed mitral valve disease

Table 21: Clinical evidence summary: Minimally invasive surgery replacement vs. standard surgery replacement

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
All-cause mortality at 12 months	Not reported				
Cardiac mortality at 12 months	134 (2 studies) in-hospital/postoperative	⨁⊖⊖⊖ VERY LOW[b,e,g] due to risk of bias, indirectness	RD 0 (-0.04 to 0.04)	0 per 1000	0 fewer per 1000 (from 40 fewer to 40 more)[a]
Intervention-related mortality at 30 days	415 (3 studies) in-hospital/postoperative	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, indirectness	RD -0.01 (-0.05 to 0.03)	0 per 1000	10 fewer per 1000 (from 50 fewer to 30 more)[a]
Health-related quality of life at 12 months	Not reported				
Onset or exacerbation of heart failure at 12 months	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
Intervention-related stroke or TIA at 30 days	281 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	OR 3.13 (0.14 to 70.31)	5 per 1000	10 more per 1000 (from 4 fewer to 256 more)
Intervention-related major bleeding at 30 days	Not reported				
Need for reintervention at 12 months	281 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[b,d,e] due to risk of bias, indirectness, imprecision	OR 0.24 (0.06 to 0.99)	49 per 1000	50 fewer per 1000 (from 80 fewer to 10 fewer)[a]
Length of hospital stay	415 (3 studies)	⨁⊖⊖⊖ VERY LOW[b,c,d,f,g] due to risk of bias, inconsistency, indirectness, imprecision		The mean length of hospital stay in the control groups was 11.5 days	The mean length of hospital stay in the intervention groups was 1.44 days lower (4.09 lower to 1.22 higher)
Rehospitalisation at 12 months	Not reported				
Intervention-related pacemaker implantation at 30 days	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard surgery replacement	Risk difference with minimally invasive surgery replacement (95% CI)
Intervention-related atrial fibrillation at 30 days	Not reported				
Intervention-related major vascular complications at 30 days	Not reported				
Prosthetic valve endocarditis at 12 months	259 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RR 1.38 (0.13 to 14.94)	11 per 1000	4 more per 1000 (from 10 fewer to 153 more)

[a]Absolute effect calculated manually using risk difference as zero events in at least one arm of one or more studies
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c]Downgraded by 1 increment as the population of all studies was indirect due to it being a mixed/unclear mitral valve disease population.
[d]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[e]Downgraded by 2 increments as the population of all studies was indirect due to it being a mixed/unclear mitral valve disease population. Also likely to be <3 months follow-up and the outcome is not well defined - may not be specifically valve reintervention.
[f]Downgraded by 1 increment as inconsistency is present which cannot be explained by subgrouping due to there only being three studies in the meta-analysis.
[g]MIDs used to assess imprecision were ±0.95

1.4.4.11 Tricuspid regurgitation

Table 22: Clinical evidence summary: Transcatheter repair + medical vs. medical alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical alone	Risk difference with transcatheter repair + medical (95% CI)
All-cause mortality at 12 months (dichotomous)	28 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW)[a,b] due to risk of bias, imprecision	RR 2 (0.78 to 5.14)	286 per 1000	286 more per 1000 (from 63 fewer to 1000 more)
Cardiac mortality (right heart failure) at 12 months (dichotomous)	28 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1.33 (0.36 to 4.9)	214 per 1000	71 more per 1000 (from 137 fewer to 835 more)
Intervention-related mortality at 30 days (in-hospital, dichotomous)	28 (1 study) in-hospital	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	OR 8.67 (0.83 to 91.1)	0 per 1000	214 more per 1000 (from 18 fewer to 447 more)[c]
Quality of life (MLWHF Q) at 12 months (continuous) Scale from: 0 to 105.	19 (1 study) 3 months	⨁⨁⊖⊖ VERY LOW [a,b,d] due to risk of bias, imprecision	NA	The mean quality of life (MLWHF Q) at 12 months (continuous) in the control groups was -7.6	The mean quality of life (MLWHF Q) at 12 months (continuous) in the intervention groups was 12.3 lower (25.54 lower to 0.94 higher)
	19		OR 0.18		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical alone	Risk difference with transcatheter repair + medical (95% CI)
Onset or exacerbation of heart failure (NYHA class worsening by 1 or 2 classes) at 12 months (dichotomous)	(1 study) 3 months	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	(0 to 9.42)	1 per 1000	91 fewer per 1000 (from 331 fewer to 149 more)[c]
Intervention-related stroke or TIA at 30 days	Not reported				
Intervention-related major bleeding (haemorrhage) at 30 days (dichotomous)	28 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	OR 7.39 (0.15 to 372.38)	0 per 1000	71 more per 1000 (from 106 fewer to 248 more)[c]
Need for reintervention at 12 months (48 h, dichotomous)	28 (1 study) 48 hours	⨁⊖⊖⊖ VERY LOW [a,b,e] due to risk of bias, indirectness, imprecision	OR 9.49 (1.19 to 75.86)	0 per 1000	286 more per 1000 (from 37 more to 535 more)[c]
Length of stay (following initial intervention)	Not reported				
Rehospitalisation (hospitalisation for HF) at 12 months (dichotomous)	28 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1 (0.31 to 3.23)	286 per 1000	0 fewer per 1000 (from 197 fewer to 638 more)
Intervention-related pacemaker implantation at 30 days	Not reported				
Intervention-related atrial fibrillation at 30 days	Not reported				
	28				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical alone	Risk difference with transcatheter repair + medical (95% CI)
Major vascular complications at 30 days (dichotomous)	(1 study) 30 days	⨁⊖⊖⊖ VERY LOW [a,f] due to risk of bias, imprecision	RD: 0.00 (-0.13 to 0.13)	0 per 1000	0 fewer per 1000 (from 130 fewer to 130 more)[c]
Prosthetic valve endocarditis at ≥12 months	Not reported				

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c]Absolute effect calculated manually using risk difference as 0 events in one or both arms of one study
[d]MIDs used to assess imprecision were ±5.00
[e]All events said to have occurred within 48 h and unclear if any further reinterventions occurred during follow-up
[f]Graded very serious imprecision as 0 events in both arms and sample size <70

See Appendix F: for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

Aortic stenosis (non-bicuspid)

Nine health economic studies with relevant comparisons were included in this review: 2 comparing only transcatheter aortic valve implantation to medical management [282, 422] and 5 comparing transcatheter aortic valve implantation to surgical aortic valve implantation.[116, 142, 381-383, 386] Two studies compared both transcatheter aortic valve implantation to medical management and transcatheter aortic valve implantation to surgical aortic valve implantation.[99, 200] These are summarised in the health economic evidence profiles below (Table 23 to Table27) and the health economic evidence tables in Appendix H:.

Mixed/unclear aortic valve disease

One health economic study with the relevant comparison was included comparing mini-sternotomy to full median sternotomy.[263] This is summarised in the health economic evidence profile below (Table 29) and the health economic evidence table in Appendix H:.

Mitral regurgitation

Three health economic studies with the relevant comparisons were included comparing percutaneous mitral valve repair with MitraClip device versus medical management.[246, 327 348] These are summarised in the health economic evidence profile below (Table 30) and the health economic evidence table in Appendix H:.

Unclear/mixed mitral valve disease

One health economic study with the relevant comparison was included comparing minimally invasive surgery to full median sternotomy[408]. This is summarised in the health economic evidence profile below (Table 30) and the health economic evidence table in Appendix H:.

Other populations

No health economic studies were included for populations with:

- aortic stenosis (bicuspid)
- aortic stenosis (mixed non-bicuspid and bicuspid or unclear)
- aortic regurgitation (non-bicuspid)
- aortic regurgitation (bicuspid)
- aortic regurgitation (mixed non-bicuspid and bicuspid or unclear)
- tricuspid regurgitation.

1.5.2 Excluded studies

Twenty-seven economic studies relating to this review question were identified but were excluded due to methodological limitations or the availability of more applicable evidence. [21, 33, 52, 61, 63, 69, 72, 83, 131, 150, 153, 158, 167, 178, 259, 269, 300, 320, 333, 338, 339, 365, 404, 423 179 116, 166]

These are listed in Appendix I: with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G:.

1.5.3 Summary of studies included in the economic evidence review

1.5.3.1 Aortic stenosis

Table 23: Health economic evidence profile: Transcatheter aortic valve implantation versus medical management (inoperable)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Orlando 2013[282] (UK)	Directly applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic model (decision tree) based on an RCT (PARTNER-1B)) • Cost-utility analysis (QALYs) • Population: People with severe AS who cannot undergo surgery[(c)] • Comparators: TAVI vs MM • Time horizon: 25 years	TAVI costs £24,147[(d)] more per person	TAVI gives 1.87 more QALYs per person	£12,900 per QALY gained	Probability TAVI cost effective (£20K threshold) : >95%. Deterministic analyses varied the proportion of people receiving each intervention. Results remained robust in all analyses.
Watt 2012[422] (UK)	Directly applicable[(h)]	Potentially serious limitations[(i)]	• Probabilistic model (Markov model) based on an RCT (PARTNER-1B)) • Cost-utility analysis (QALYs) • Population: People with severe AS who cannot undergo surgery[(c)] • Comparators: TAVI vs MM • Time horizon: 10- years	TAVI costs £25,200[(j)] more per person	TAVI gives 1.56 more QALYs per person	£16,200 per QALY gained	Probability TAVI is cost effective (£20K threshold): 100%. Deterministic sensitivity analyses showed that results were most sensitive to short-term treatment effect and the cost of initial hospitalisation. Results were robust to changes in hospitalisation costs and adverse event rates.

Abbreviations: AS: aortic stenosis; ICER= incremental cost-effectiveness ratio; MM: medical management; QALY= quality-adjusted life years; RCT= randomised controlled trial; TAVI: transcatheter aortic valve implantation

(a) UK based cost utility analysis

(b) Utility data source refers to a paper that assesses both SF-36 and EQ-5D, it is not specified if EQ-5D or SF-36 has been extracted from the paper. Furthermore this paper specifically assesses utility of a Dutch population with mechanical aortic valve replacement. Observational data is used to assess the incidence of adverse events within 30 days. The PARTNER-B trial only used the Edwards SAPIEN heart-valve system; therefore generalisability of the results to other valves may be limited.

(c) 'Cannot undergo surgery' defined as those with coexisting conditions associated with a predicted probability of ≥50% of death after surgery or a serious irreversible condition

(d) 2010 GBP costs. Cost components incorporated: adverse events (stroke, MI, arrhythmia, cardiac tamponade, bleeding, heart failure or shock, valve embolism, respiratory failure, renal dialysis, vascular complications), initial hospital stay and procedure cost.

(e) UK based cost utility analysis

(f) Utility data source refers to a paper that assesses both SF-36 and EQ-5D, is not specified if EQ-5D or SF-36 has been used. Furthermore, this paper specifically assesses utility of those with mechanical aortic valve replacement. Utility of stroke considered the same as death. Discounting factor, if used, not reported for both costs and outcomes. Observational data was used to inform parameters where RCT evidence was not available. Nursing home costs appear to be taken from a PSSRU publication from 1996, there is no description of inflating costs to or near the year of publication. The PARTNER-B trial only used the Edwards SAPIEN heart-valve system; therefore generalisability of the results to other valves may be limited.

(g) NR so assumed to be the same year as publication (2013 GBP). Cost components incorporated: TAVI and AVR devices (AVR included where conversion was necessary) and procedures, length of stay, hospitalisations pertaining to NYHA classes, medication costs.

(h) UK based cost utility analysis

(i) Some parameters were informed by non-randomised data. The PARTNER-B trial only used the Edwards SAPIEN heart-valve system; therefore generalisability of the results to other valves may be limited. Appear to use the costs of the Medtronic CoreValve system, although the clinical data pertains to the Edwards SAPIEN valve system.

(j) 2010 GBP costs. TAVI and AVR devices (AVR included where conversion was necessary) and procedures, length of stay, hospitalisations pertaining to NYHA classes, medication costs.

Table 24: Health economic evidence profile: Transcatheter aortic valve implantation versus standard therapy and transcatheter aortic valve implantation versus surgical aortic valve implantation (inoperable and high operative risk)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Doble 2013[99] (Canada)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic model (Markov model) based on 1 RCT for each of 2 cohorts (PARTNER-1A and 1B) • Cost-utility analysis (QALYs) • Populations: ○ People with severe AS who cannot undergo surgery[(c)] ○ People with severe AS who have a high risk of surgical complications[(d)] • Comparators for inoperable and high risk cohorts: TAVI vs Standard therapy and TAVI vs SAVR • Time horizon: 20- years	**Inoperable** TAVI costs £17,838 more per person **High risk** TAVI costs £6,412 more per person	**Inoperable** TAVI gives 0.85 more QALYs per person **High risk** TAVI gives 0.102 less QALYs per person	**Inoperable** TAVI costs £29,506 per QALY gained **High risk** TAVI is dominated by SAVR (TAVI has higher costs and lower QALYs)	Probability TAVI cost effective for inoperable and high risk cohorts (£20K threshold): NR and NR (but 44.1% and 11.6% probability of being cost effective at a £28K threshold). Deterministic analyses for the inoperable cohort showed that the model was most sensitive to the procedural costs and 1-year mortality rates for both treatments. TAVI remained dominated by SAVR in all deterministic analyses in the high risk cohort.

Abbreviations: *AS: aortic stenosis; ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation*

(a) 2013 Canadian health care payer perspective may not reflect current UK context; QALYs derived from EQ-5D.

(b) A single RCT (PARTNER-B) trial was used to inform treatment effect for the TAVI versus standard therapy cohort (the only eligible RCT included in the clinical review for this comparison). A single RCT (PARTNER-A) trial was used to inform treatment effect for TAVI versus SAVR (1/7 eligible included in the clinical review for this comparison). The PARTNER-A and -B trials only use the Edwards SAPIEN valve, generalisability to other valves may be limited. Clinical event rates for (stroke, myocardial infarction and kidney injury) were assumed to remain constant after year 1 of the model due to a lack of data. Rates of temporary and permanent dialysis were also assumed to be the same for all 4 treatments due to a lack of data.

(c) 'Cannot undergo surgery' defined as those with coexisting conditions associated with a predicted probability of ≥50% of death after surgery or a serious irreversible condition

(d) High risk defined as patients with a predicted risk of operative mortality of ≥15% or a society of Thoracic Surgery risk score of ≥10%

Table 25: Health economic evidence profile: Transcatheter aortic valve implantation versus medical therapy and transcatheter aortic valve implantation surgical aortic valve implantation (inoperable and intermediate operative risk)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Kodera 2018[200] (Japan)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Two probabilistic models (Markov model) ran separately for 2 cohorts (based on the PARTNER-1B and PARTNER- 2A RCTs) • Cost-utility analysis (QALYs) • Populations: ○ People with severe AS who have cannot undergo surgery[(c)] ○ People with severe AS who have an intermediate risk of surgical complications[(d)] • Comparators for inoperable ○ TAVI vs Medical therapy • Comparators for intermediate risk ○ TAVI vs SAVR • Time horizon: 10- years	**Inoperable** TAVI costs £43,391 more per person **Intermediate risk** TAVI costs £11,731 more per person	**Inoperable** TAVI gives 1.75 more QALYs per person **Intermediate risk** TAVI gives 0.22 more QALYs per person	**Inoperable ICER** TAVI costs £26,673 per QALY gained **Intermediate risk ICER** TAVI costs £51,210 per QALY gained	Probability TAVI cost effective for inoperable and intermediate risk cohorts (£20K threshold): NR and NR (but 60% and 46% probability of being cost effective at £34K threshold) Deterministic sensitivity analyses showed that both models were sensitive to the 1 year mortality rate of TAVI and the cost of the TAVI procedure. TAVI was cost effective for the intermediate operative risk cohort when a 20- year time horizon was used.

Abbreviations: *AS: aortic stenosis; ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation*

(a) Japanese healthcare perspective may not reflect UK NHS

(b) The PARTNER-A trial only uses the Edwards SAPIEN valve so generalisability to other valves may be limited. A single RCT (PARTNER-2A) trial was used to inform treatment effect for TAVI versus SAVR (1/7 eligible included in the clinical review for this comparison). The PARTNER- 2A trial only uses the Edwards SAPIEN XT valve so generalisability to other valves may be limited. The methodology used for discounting is unclear and the discount rate applied is 2% (instead of 3.5%). Probabilistic sensitivity analysis conducted using a threshold above the £30,000 threshold recommended in the NICE Reference Case. Mortality partly informed by observational data.

(c) 'Cannot undergo surgery' defined as those with coexisting conditions associated with a predicted probability of ≥50% of death after surgery or a serious irreversible condition

(d) Intermediate operative risk defined as those who have a STS risk score of >4% and<8%

1.5.32 Table 26: Health economic evidence profile: Transcatheter aortic valve implantation versus surgical aortic valve implantation (intermediate and high operative risk)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Tarride 2019[386] (Canada)	Partially applicable [(a)]	Potentially serious limitations[(b)]	• Probabilistic model based on PARTNER IA, PARTNER IIA and PARTNER • Cost-utility analysis (QALYs) • Population: Patients with severe aortic stenosis undergoing SAVR or TAVI with intermediate or high operative risk • Comparators: SAVR vs TAVI Time horizon: 15 years (in the base case)	**High risk** TAVI costs £4,062 more per person [(c)] **Intermediate risk** TAVI costs £7,433 more per person[(f)]	**High risk** TAVI gives 0.43 more QALYs per person **Intermediate risk** TAVI gives 0.48 more QALYs per person	**High risk** TAVI costs £9,510 per QALY gained **Intermediate risk** TAVI costs £15,533 per QALY gained	**High risk** Probability TAVI cost effective (£27,585K/55,170K threshold): 93%/99% **Intermediate risk** Probability TAVI cost effective (£27,585K/55,170K threshold): 91%/99% Probabilistic and deterministic sensitivity analysis conducted. The ICER was found to be sensitivity to the length of the time horizon assumed, becoming higher than Canadian threshold when the analysis was conducted for a period of 5 years.

Abbreviations: RCT= randomised controlled trial, QALY= quality adjusted life years; TAVI= Transcatheter aortic valve implantation; SAVR= Surgical aortic valve replacement

(a) Canadian health care perspective

(b) Several outcomes included but only a few modelled as Markov states even though some of those have important implication on quality of life and mortality. Data from PARTNER I and PARTNER II, not a systematic review. Reintervention was not modelled despite available data indicates that it tends to occur earlier with TAVI. Mortality and clinical evidence based on non-randomized data. Cost data not adjusted for differences in baseline and subject to the peculiarities of patients undergoing SAVR or TAVI

(c) 2018 Canadian dollar converted to UK pounds.[281]. Cost components incorporated: Cost of the device, post-procedural inpatient costs, physician fees related to the procedure and to specialist consultations during the inpatient stay, along with workup costs that occurred in an emergency room or ambulatory setting just prior to admission and cost of medicines.

Table27: Health economic evidence profile: Transcatheter aortic valve implantation versus surgical aortic valve implantation (intermediate operative risk)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Goodall 2019[142] (France)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic model (Markov model) based on an RCT (PARTNER-2)) • Cost-utility analysis (QALYs) • Population: People with severe AS who have an intermediate risk of surgical complications[(c)] • Comparators: TAVI vs SAVR • Time horizon: 15- years	TAVI saves £386[(d)] per person	TAVI gives 0.41 more QALYs per person	TAVI dominates SAVR	Probability TAVI cost effective (£20K threshold): NR (but 100% probability of being cost effective at a threshold of £13.2K). Results were robust to all deterministic sensitivity analyses
Tam 2018A[382] (Canada)	Partially applicable[(e)]	Potentially serious limitations[(f)]	• Probabilistic model (Markov model) based on an RCT (PARTNER-2)) • Cost-utility analysis (QALYs) • Population: People with severe AS who have an intermediate risk of surgical complications[(c)]	TAVI costs £5,919[(g)] per person	TAVI gives 0.23 more QALYs per person	£25,856 per QALY gained	Probability TAVI cost effective (£20K threshold): NR (but 52.7% probability of being cost effective at a threshold of £28K) A series of deterministic sensitivity analyses found that it was most sensitive to the cost of the TAVI valve

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			• Comparators: TAVI vs SAVR • Time horizon: 15- years				system, length TAVI ICU stay and the peri-procedural mortality rate of TAVI and SAVR.
Tam 2018B[383] (Canada)	Partially applicable[(h)]	Potentially serious limitations[(i)]	• Probabilistic model (Markov model) based on an RCT (SURTAVI)) • Cost-utility analysis (QALYs) • Population: People with severe AS who have an intermediate risk of surgical complications[(j)] • Comparators: TAVI vs SAVR • Time horizon: Lifetime	TAVI costs £6,343 [(k)] more per person	TAVI gives 0.15 more QALYs per person	£43,055 per QALY gained	Probability TAVI cost effective (£20K threshold): NR (but 52.9% probability of being cost effective at a threshold of £28K) A series of deterministic sensitivity analyses found that it was most sensitive to the cost of the TAVI valve and both TAVI and SAVR 30 day mortality.

Abbreviations: AS: aortic stenosis; ICER= incremental cost-effectiveness ratio; MM: medical management; QALY= quality-adjusted life years; RCT= randomised controlled trial; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation

(a) French cost utility analysis that may not fully reflect a UK NHS perspective

(b) Observational data was used to inform health outcomes where RCT data was not available. A discount rate of 4.0% was applied to costs and health outcomes (instead of 3.5% as per NICE reference case). Treatment effect derived from a single RCT(1/7 eligible included in the clinical review that compared TAVI versus SAVR)

(c) Intermediate risk of surgical complications defined as those who have a STS risk score of >4% and <8%

(d) 2016 Euros presented here as 2016 GBP converted to UK pounds.[281]. Cost components incorporated: Index admission costs for TAVI and SAVR. Cost of the TAVI device was added to this separately. Cardiac rehabilitation, hospitalisations, reintervention and adverse events (major stroke, TIA. Major bleeding, major vascular complication, atrial fibrillation, renal replacement therapy, myocardial infarction, endocarditis, pacemaker implantation.

(e) Canadian cost utility analysis that may not fully reflect a UK NHS perspective

(f) A single RCT (PARTNER-2) trial was used to inform treatment effect (1/7 eligible included in the clinical review). The proportion of patients with acute kidney injury progressing to dialysis was not provided in the PARTNER 2 Trial and was estimated from the PARTNER 1A trial that used a different valve. Some observational data was used to inform health outcomes where RCT data was not available. A discount rate of 1.5% was applied to costs and health outcomes (instead of 3.5% as per NICE reference case).2016 Canadian dollars presented here as 2016 GBP converted to UK pounds.[281]. Cost components incorporated: Procedure costs (valve, ward stay, ICU stay, staff, anaesthesia, insertion of temporary pacemaker wire, angiogram, angioplasty, and catheterisation). Long term costs (disabling and non-disabling stroke, hospitalisation, major bleeding, vascular injury, acute kidney injury, atrial fibrillation.

(g) Canadian cost utility analysis that may not fully reflect a UK NHS perspective

(h) A single RCT (SURTAVI) trial was used to inform treatment effect (1/7 eligible included in the clinical review). utility data was obtained from an RCT (CoreValve trial) that looked at patients who were if high risk (as opposed to intermediate risk). A discount rate of 1.5% was applied to costs and health outcomes (instead of 3.5% as per NICE reference case).

(i) 2016 Canadian dollars presented here as 2016 GBP. Cost components incorporated: Procedure costs (Valve, ward stay, ICU stay, staff, anaesthesia, insertion of temporary pacemaker wire, angiogram, angioplasty, and catheterisation). Peri-procedural complications. Long term disabling and non-disabling stroke

1.5.34 Table 28: Health economic evidence profile: Transcatheter aortic valve implantation versus surgical aortic valve implantation (low operative risk)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Tam 2020[381] (Canada)	Partially applicable [(a)]	Potentially serious limitations[(b)]	• Probabilistic model based on PARTNER 3, and Evolut trial • Cost-utility analysis (QALYs) • Population: Patients with severe aortic stenosis undergoing SAVR or TAVI low risk Comparators: Balloon-expandable TAVI Vs Self-expandable TAVI Vs SAVR Time horizon: Lifetime	Balloon-expandable TAVI costs £1,590[(c)] more per person compared to SAVR Self-expandable TAVI costs £2,917[(i)] more per person compared to SAVR[)]	Balloon-expandable TAVI gave 0.1 extra QALYs per person compared to SAVR Self-expandable TAVI gave 0.08 extra QALYs per person compared to SAVR	Balloon-expandable TAVI costs £15,900 per QALY gained compared to SAVR	PARTNER 3 data only; Balloon-expandable TAVI costs **£38,118** per QALY gained compared to SAVR Self-expandable TAVI costs **£57,581** per QALY gained compared to SAVR Evoult data only; Balloon-expandable TAVI costs is **dominant** compared to SAVR Self-expandable TAVI costs **£14,717** per QALY gained compared to SAVR

Abbreviations: RCT= randomised controlled trial, QALY= quality adjusted life years; TAVI= Transcatheter aortic valve implantation; SAVR= Surgical aortic valve replacement

(a) Canadian third-party payers' perspective

(b) Non-UK perspective and not systematic review.

(c) The calculated incremental costs and QALYs vary from the reported ones, the ones presented here in the table are the calculated ICER. Third party payer perspective. Non-UK study. Limited sensitivity analysis. As the sources used where for older population with a mean age of 74 years the results may not be generalisable to younger populations. 2019 Canadian dollars converted to UK pounds.[281]. Upfront procedural costs (TAVI systems, valve, cardiology fees, surgeon fees, surgical assistant fees, anaesthesiologist fee, ward and ICU stay).

1.5.3.4 Mixed/unclear aortic valve disease

Table 29: Health economic evidence profile: Mini-sternotomy versus Full median sternotomy

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Nair 2018[263] (UK)	Directly applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic within-RCT analysis (MINI-STERN Trial) • Cost-utility analysis (QALYs) • Population: Adult patients undergoing first-time isolated AVR were included • Comparators: Mini-sternotomy versus Full median sternotomy • Time horizon: 12-months	Mini-sternotomy costs £2,154[(d)] more per person	Mini-sternotomy gives 0.122 less QALYs per person	Mini-sternotomy is dominated by full median sternotomy (Mini-sternotomy had higher costs and lower QALYs)	Probability mini-sternotomy is cost effective (£20k/£30K threshold): NR/5.1%. Deterministic sensitivity analyses found that results robust to all analyses apart from the complete case analysis where Mini-sternotomy was cost effective.

Abbreviations: AVR: aortic valve replacement; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); QALYs: quality-adjusted life years; RCT= randomised controlled trial

(a) UK cost-utility analysis. The study does not compare all interventions available (transcatheter interventions) to this population.

(b) Time horizon of 12 months may not fully capture costs and QALYs. Unclear what the adjusted QALY gain is for each intervention. Intervention effect is estimated from a single RCT.

(c) 2015 GBP costs. Cost components incorporated: Primary admission (theatre use, surgical items, critical care, cardiac ward, physio- and occupational therapy, rehabilitation, acute hospital). Post initial stay costs (hospital re-admission, follow up tests, follow up healthcare visits, drugs).

1.5.3.5 Mitral regurgitation

Table 30: Health economic evidence profile: Percutaneous mitral valve repair versus medical management

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Mealing 2013[246] (UK)	Directly applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic model (decision tree) based on registry data (EVEREST 2 High Risk Registry) • Cost-utility analysis (QALYs) • Population: Patients with severe mitral regurgitation ineligible for surgical intervention[(c)] • Comparators: Percutaneous mitral valve repair versus medical management • Time horizon: 5 years	Percutaneous mitral valve repair costs £26,989[(c)] more per person	Percutaneous mitral valve repair gives 1.22 more QALYs per person	£22,153 per QALY gained	Probability transcatheter mitral valve repair is cost effective (£20K/£30K threshold): 37%/93%. The deterministic analyses showed that when the time horizon was 10 years, the ICER was £14,800 per QALY gained. The model was relatively insensitive to procedural costs, device costs and mortality.
Sakamaki 2019[327] (Japan)	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Probabilistic model (Markov model) based on a propensity score matching study (Velazquez 2015) comparing 4 observational studies • Cost-utility analysis (QALYs) • Population with symptomatic severe MR at high surgical risk • Comparators: percutaneous mitral valve repair with	MitraClip costs £19,558 more per person[(f)]	MitraClip gives 1.42 more QALYs per person	£13,549 per QALY gained	Probability MitraClip cost effective (£34,415 threshold): 96.7% The deterministic analyses showed that MitraClip ceases to be cost-effective when the HR for Overall Survival for MitraClip procedure against medical management exceeds 0.97. The model is sensitive to the assumption on rate of hospitalisation in the two arms.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			MitraClip versus medical management				
Shore 2020[348] (UK)	Directly applicable	Minor limitations(g)	• Probabilistic model (partition survival model) based on COAPT randomized trial[367] • Cost-utility analysis (QALYs) • Population with severe functional MR at high surgical risk or deemed inoperable • Comparators: transcatheter mitral valve repair with MitraClip versus guideline directed medical therapy	MitraClip costs £32,267 more per person(h)	MitraClip gives 1.07 more QALYs per person	£30,057 per QALY gained	Probabilistic MitraClip cost effective (£20k/£30k threshold): 0%/65% The deterministic analyses showed that the results are sensitive to the HR for mortality, to the rate of repeat intervention and MV surgery and to the cost of the procedure.

Abbreviations: EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); QALYs: quality-adjusted life years

(a) The study does not include mitral valve replacement as a comparator

(b) Treatment effect was informed by the EVEREST II High Risk Registry, which is a prospective, single arm registry; it is non-randomised and therefore not included in the clinical review.

(c) 2011 GBP costs. Cost components incorporated: Drug costs, MitraClip delivery system, Hospitalisation costs including: ICU stay, non-ICU stay, stroke, cardiovascular surgery, myocardial infarction, renal failure, deep wound infection

(d) The study was conducted from the perspective of the Japanese health care payer

(e) Treatment effect was informed by a propensity score matching study, not a RCT. The assumption that no adverse event occurs in the medical management arm is unrealistic albeit conservative. Resource usage was sought from expert opinion instead of a trial

(f) 2018 Japanese Yen reported as 2018 UK pounds. Cost components incorporated: Device cost (MitraClip), technical fee, cost other than device cost and technical fee, MitraClip procedure hospitalisation, MV surgery, congestive heart failure hospitalisation, treatment cost for MitraClip complications (vascular complications, major bleeding, non-cerebral thromboembolism, drug cost, follow-up cost, adverse events costs (MI, stroke, renal failure, non-elective cardiovascular surgery, mechanical ventilation, GI complication requiring surgery, septicemia, blood transfusion).

(g) Treatment effect was derived by a single RCT rather than a systematic review. Some outcomes with potentially long-term consequences on survival, NHS resource use and QALYs were not modelled as long-term health states. The proportion of people in each NYHA was assumed to be constant beyond the last follow-up

(h) 2020 GBP costs. Cost components incorporated: Device cost (MitraClip), pre-procedural cost, peri-procedural cost, cost of the initial hospital stay, rehabilitation cost, hospitalization cost, MV surgery and repeat MV intervention cost, background medication cost per month NYHA, outpatient care cost per month NYHA, replacement ICD/CRT cost, cost of stroke, cost of MI, cost of heart transplant

1.5.32 Mixed/unclear mitral disease

Table 31: Health economic evidence profile: Full median sternotomy versus minimally invasive surgery

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Verbrugghe 2016[341] (Belgium)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Retrospective cohort analysis • Cost comparison • Population: People who went isolated mitral valve • Comparators: Full median sternotomy versus minimally invasive surgery • Time horizon: initial inpatient stay	Minimally invasive surgery costs £411 less per person	Minimally invasive surgery had 27 less complication occurring [(c)]	£411 less per person	No sensitivity analysis was conducted

Abbreviations: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); QALYs: quality-adjusted life years; RCT= randomised controlled trial

(a) Cost comparison from a single Belgian hospital perspective.
(b) Cost of implants was excluded. Non-randomised retrospective analysis. Quality adjusted life years not used as an outcome. Sensitivity analyses not conducted
#1. Health outcomes: included mortality, any complication, reoperation, arrhythmia, neurologic complication, renal complication, pneumonia and wound infection

1.5.4 Health economic modelling

Two health economics models were developed to assess the cost-effectiveness of TAVI compared to standard surgery in operable people with aortic stenosis and edge-to-edge repair with MitraClip device in inoperable people with severe functional mitral regurgitation.

1.5.4.1 MitraClip model

Population and strategies

The model population were people with severe mitral regurgitation secondary to heart failure and the strategies compared were

- Medical management
- Edge-to-edge mitral valve repair with MitraClip device

Methods and data sources

Model structure

- A two-part model was developed which included a decision tree to model post-procedural outcomes (up to 30 days) followed by a Markov model for long-term extrapolation of outcomes and costs.
- The Markov model was run for 30 cycles simulating 30 years of life.
- The decision tree model includes the following outcomes: stable, major bleeding, vascular complication, stroke and dead. Major bleeding and vascular complication were assumed to be only temporary states. Stroke was assumed to have long-term consequence and modelled as a Markov state
- The Markov model includes the following outcomes: heart transplant first year, heart transplant >1 year, stable, reintervention, stroke and post-stroke and dead.
- Reintervention, heart transplant first year and stroke were assumed to be tunnel states, so people spend only one cycle in those states before moving to the next state
- People transiting to the reintervention state move to a new decision tree model simulating the outcomes of the new intervention and then re-enter the Markov model in the states determined by the decision tree
- Both people in the medical management and MitraClip arm can undergo a reintervention, which is assumed to be always a MitraClip.

Treatment effect and data sources

- Treatment effects were sought from the COAPT trial since it better reflects the population of interest
- Mortality rates after MitraClip were taken from the 3-year results of the COAPT trial and extrapolated over 30 years using a Weibull function
- Utility scores were extracted from the COAPT trial and converted to EQ-5D using a mapping algorithm
- For post-procedural outcomes, an UK registry (CtE) on MitraClip was used and supplemented with data from the Mitra-FR trial when necessary

Costs

- Cost for the MitraClip device was extracted from the Commission through Evaluation (CtE) study. A cost of £32,910 was used in the base case scenario while an upper case estimation of £34,500 and a lower case estimation of £29,900 were both tested in the sensitivity analysis
- The cost of the drugs for the medical management of heart failure and immunosuppressive therapy were calculated using BNF and the Prescription Cost Analysis database. The price and dosage of the drugs were informed from the BNF and the Prescription Cost Analysis was used to calculate the average cost per mg

- The cost associated with stroke and post-stroke was extracted from an UK costing study on the burden of stroke in the UK and inflated to 2018/2019
- Other costs, such as the cost associated with a heart failure hospitalisation or of a major bleeding and vascular complication events were recovered from the NHS Reference Costs 2018/2019

Results

The base case results can be found in Table 32 and table 33 whereas table 34 offers a breakdown of costs. Mitraclip was more expensive than medical management but has a greater quality of life treatment effect. At a threshold of £20,000 per QALY, MitraClip was not cost-effective and it was slightly above the threshold of £30,000 per QALY gained.

Table 32: Base case results – costs (probabilistic)

Cost	Medical management	Mitraclip	Difference (Mitraclip – MM)
MitraClip	£32,910	£0	£32,910
HF drugs	£1,061	£627	£434
Vascular complications	£47	£0	£47
Bleeding	£30	£20	£9
Stroke	£412	£31	£380
Hospitalisation	£6,537	£10,157	-£3,620
Reintervention	£2,594	£3,282	-£688
Heart transplant	£1,267	£3,342	-£2,074
Immunosuppressive drugs	£487	£1,385	-£899
Total	£45,345	£18,845	£26,499

Table 33: Base case results - cost-effectiveness (probabilistic)

	Medical management	Mitraclip
Costs	£18,799	£45,304
QALYs	2.05	2.92.
Cost per QALY gained (vs conservative management)	-	£30,283
Incremental net monetary benefit (INMB)*	0	-£11,043
Incremental net monetary benefit (INMB)**	0	-£2,308
Probability cost-effective at 20k threshold	95%	5%
Probability cost-effective at 30k threshold	53%	47%

*at a threshold of £20,000 per QALY gained

**at a threshold of £30,000 per QALY gained

Table 34: cost breakdown per patient (probabilistic)

Age	Incremental cost	Incremental QALYs	Cost per QALY gained
MitraClip	£32,910	£0	£32,910
Heart failure drugs	£1,061	£628	£433
Vascular complications	£47	£0	£47
Bleeding	£29	£21	£9
Stroke	£418	£32	£386
Hospitalisation	£6,529	£10,135	-£3,606
Reintervention	£2,580	£3,277	-£697
Heart transplant	£1,250	£3,328	-£2,078
Immunosuppresssive drugs	£480	£1,379	-£899
Total cost	£45,304	£18,799	£26,505

Several one-way sensitivity analyses were conducted and are illustrated in table 35. The incremental cost-effectiveness ratio was found to be sensitive to the price of the intervention and to the assumption on utility and mortality distribution. Overall, they suggest that incremental cost-effectiveness ratio of MitraClip compared to medical management is above £30,000 per QALY gained.

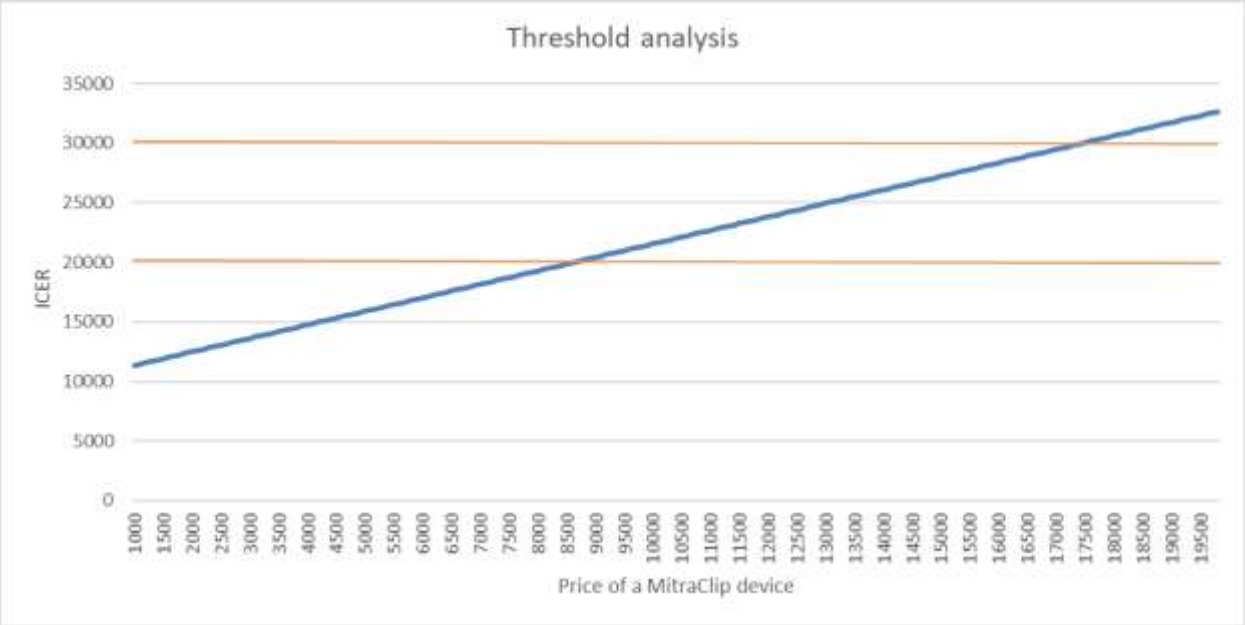
Table 35: Scenario analysis (deterministic)

Scenario	Incremental cost	Incremental QALYs	Cost per QALY gained
Deterministic results	£28,513	0.88	£32,315
Probabilistic results	£26,505	0.87	£30,283
Lower case Mitraclip cost	£25,537	0.88	£28,942
Upper case Mitraclip cost	£30,085	0.88	£34,096
No transplant	£30,196	0.92	£32,818
CtE data	£28,374	0.83	£34,033
Utility difference is persistent	£28,513	1.04	£27,428
Exponential distribution for mortality	£28,457	0.95	£30,079
Benefits last for the duration of the trial only	£27,169	0.56	£48,262
Exclude vascular complication	£28,466	0.88	£32,261

A threshold analysis on the price of a MitraClip device was conducted to determine the threshold value of the price at which MitraClip becomes cost-effective at a threshold of £20,000. This was achieved through excel by varying the price of the device from £1,000 to

£20,000 and looking at the corresponding incremental cost effectiveness ratio. The results are shown in figure 1.

Figure 1: MitraClip price threshold analysis



The results of the analysis demonstrate that MitraClip intervention becomes cost effective at a threshold £30,000 when the price drops below £17,500 (equal to a discount of 11.62%) and cost effective at a threshold of £20,000 when the price lies below £8,700 (equal to a discount of 56%). These price values are considerable lower than the price currently reported in the NHS Supply Chain Catalogue of £19,800.

1.5.4.2 TAVI model

Population and strategies

The model population were adults with operable aortic stenosis (non-bicuspid) requiring intervention at intermediate or high surgical risk and the following strategies were compared:

- Standard (surgical) aortic valve replacement (SAVR) with biological valves
- Transcatheter aortic valve implantation (TAVI)

Methods and data sources

Model structure

- A two-part model was developed which included a decision tree to model post-procedural outcomes (up to 30 days) followed by a Markov model for long-term extrapolation of outcomes and costs.
- The Markov model was run for 30 cycles simulating 30 years of life.
- The decision tree model includes the following outcomes: stable, major bleeding, vascular complication, stroke, renal injury requiring dialysis, pacemaker implantation, mild paravalvular leak (PVL), moderate/severe paravalvular leak and dead. Major bleeding and vascular complication were assumed to be only temporary states. Stroke, dialysis, pacemaker and PVL were assumed to have long-term consequence and modelled as a Markov state

- The Markov model includes the following outcomes: stroke, post-stroke, dialysis, SVD requiring reintervention, mild PVL, moderate/severe PVL and dead.
- Reintervention and stroke were assumed to be tunnel states, so people spend only one cycle in those states before moving to the next state
- People transiting to SVD requiring reintervention state move to a new decision tree model simulating the outcomes of the new intervention and then re-enter the Markov model in the states determined by the decision tree
- Reintervention is assumed to be an additional surgery or TAVI based on the current activity level in England

Treatment effect and data sources

- Relative treatment effects were based on a meta-analysis of the papers included in the clinical review. Studies referring to different risk groups were pooled together
- Baseline probabilities after SAVR were based on the papers included in the clinical review. Due to sample size issues, most of the probabilities were pooled together between intermediate- and high-risk group with the exception of the probability of dying which is different in the two risk groups.
- Mortality was based on a study[239] comparing mortality in the UK TAVI registry with the one of the general population
- Utility score were extracted from Gleason 2018[135] and Baron 2018[43] for, respectively, high risk and intermediate risk people

Costs

- The cost of a SAVR and TAVI interventions were sought from the NHS Reference Costs 2018-2019. The cost associated with hospital stay and ICU were recalculated using the data provided by the clinical studies and added to cost of the procedure alone.
- The cost of a biological valve was already included in the HRG for SAVR. The cost of a TAVI valve was extracted from the NHS Supply Chain Catalogue - £20,280. Other prices of the valve were tested in the sensitivity analysis.
- The cost associated with rehabilitation in a rehab centre or at home was sought from the Intermediate Care audit 2017
- The cost associated with stroke and post-stroke was extracted from an UK costing study on the burden of stroke in the UK and inflated to 2018/2019
- Other costs, such as the cost associated with a heart failure hospitalisation or of a major bleeding and vascular complication events were recovered from the NHS Reference Costs 2018/2019

Results

The base case results can be found in Table 36 and 37 whereas table 38 illustrates a breakdown of the cost of a 70 years old patient with high risk. TAVI is more costly but has a great quality of life treatment effect. The incremental cost-effectiveness ratio suggests that TAVI in England is not cost-effective at a £20,000 or £30,000 threshold.

Table 36: base case results (deterministic)

Age	Incremental cost	Incremental QALYs	Cost per QALY gained
Intermediate risk			
60	£14,670	0.10	£142,162
70	£13,967	0.10	£134,874
80	£13,387	0.10	£129,343

Age	Incremental cost	Incremental QALYs	Cost per QALY gained
90	£12,444	0.09	£136,796
High risk			
60	£13,147	0.12	£111,487
70	£12,392	0.12	£102,634
80	£11,767	0.12	£97,023
90	£10,716	0.11	£100,335

Table 37: Base case results - cost-effectiveness (80 years old high-risk probabilistic)

	SAVR	TAVI
Costs	£31,994	£43,613
QALYs	4.04	4.17
Cost per QALY gained (vs conservative management)	-	£92,945
Incremental net monetary benefit (INMB)*	0	-11,157,999
Incremental net monetary benefit (INMB)**	0	-10,090,934
Probability cost-effective at 20k threshold	100%	0%
Probability cost-effective at 30k threshold	97%	3%

*at a threshold of £20,000 per QALY gained

**at a threshold of £30,000 per QALY gained

Table 38: cost breakdown 80 years old high-risk patient (probabilistic)

Age	TAVI	SAVR	Difference (TAVI-SAVR)
Intervention	£32,067	£21,957	£10,110
Cost rehab	£89	£941	-£852
Vascular complications	£158	£56	£102
Bleeding	£296	£553	-£257
Pacemaker implantation	£402	£164	£238
Stroke	£2,575	£2,494	£82
Dialysis	£1,621	£2,810	-£1,189
Reintervention	£4,017	£1,335	£2,682
Hospitalisation	£2,010	£1,575	£434
Echo	£377	£109	£268
Total	£43,613	£31,994	£11,619

Several one-way sensitivity analyses were conducted and are illustrated in table 3. The incremental cost-effectiveness ratio was found to be sensitive to the price of the valve, to the assumption on PVL and reintervention rate. When a most favourable scenario to TAVI was

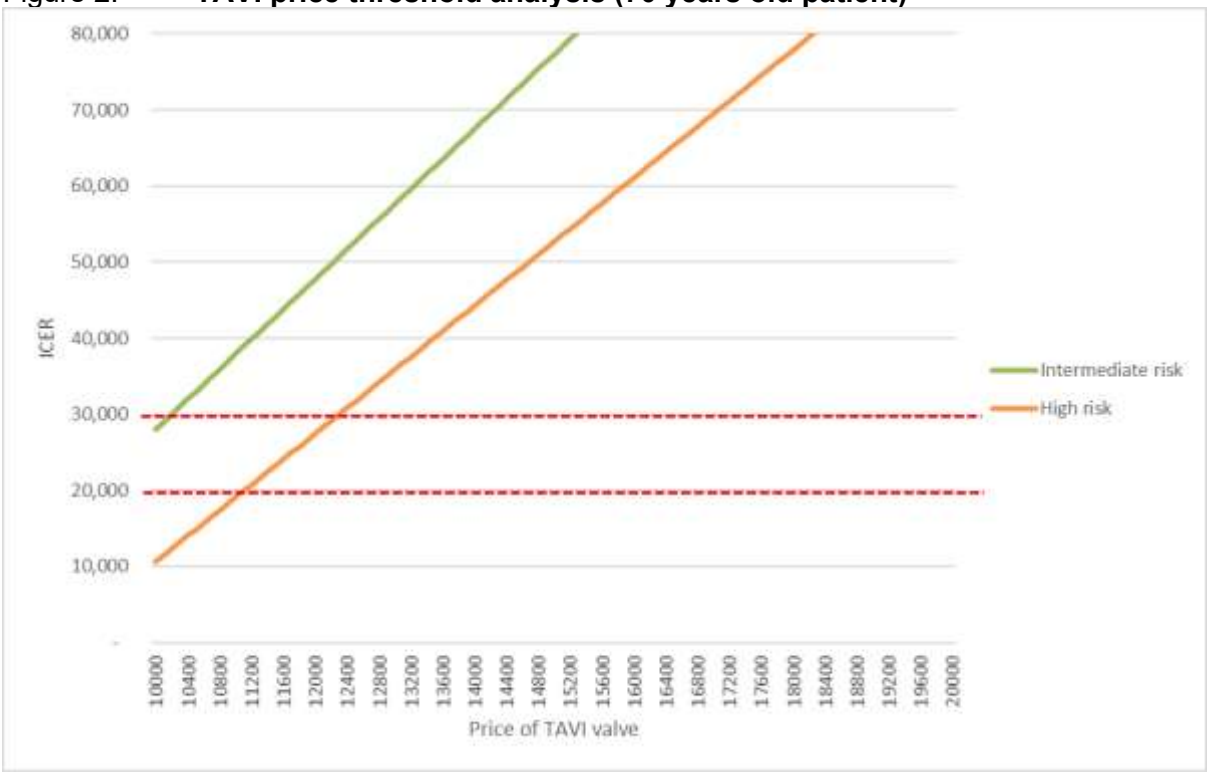
tested with no effect of PVL on mortality, same reintervention rate and no additional cost for pacemaker, the incremental cost-effectiveness ratio was found to lie below the threshold of £30,000 similarly as other studies with similar assumptions found.

Table 39: one-way (scenario) sensitivity analyses (70 years old high-risk patient)

Scenario	Incremental cost	Incremental QALYs	Cost per QALY gained
Deterministic results	£11,767	0.121	97,023
Probabilistic results	£11,619	0.125	£92,945
13-years time horizon	£11,141	0.12	£93,752
No effect of PVL on mortality	£11,767	0.16	£74,004
Mild and moderate PVL affect mortality	£11,675	0.06	£200,778
Valve discounted	£9,650	0.14	£67,788
Valve target price	£7,609	0.14	£53,451
Pacemaker cost included in the HRG	£11,654	0.14	£81,868
Same reintervention rate	£8,620	0.12	£69,220
Most favourable scenario	£4,286	0.16	£25,993

A threshold analysis on the price of a TAVI valve was conducted to determine the threshold value of the price at which a TAVI procedure becomes cost effective in intermediate and high-risk patients in England. This was achieved through excel by varying the price of the valve from £10,000 to £20,000 and looking at the corresponding incremental cost effectiveness ratio. The results are presented in figure 2.

Figure 2: **TAVI price threshold analysis (70 years old patient)**



The results of the analysis showed that for intermediate-risk patients TAVI becomes cost effective at a threshold of £30,000 per QALY gained when the price drops below £10,200. For high-risk patients TAVI becomes cost effective when the price of the valve ranges between £11,000 and £12,400. This is equal to a discount of around 39%-45%. This price is not too distant from the price TAVI is currently purchased in other developed countries, hence, if the price in the UK drops to similar levels, TAVI may become cost effective at least for high-risk patients.

1.6 Evidence statements

1.6.1 Clinical evidence statements

See the summary of evidence in Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, Table 16, Table 17, Table 18, Table 19, Table 20, Table 21 and Table 22.

1.6.2 Health economic evidence statements

- Two cost-utility analyses found that TAVI was cost effective compared to medical management for treating aortic stenosis in an inoperable population (ICERs: £12,900 per QALY gained and £16,200 per QALY gained respectively). These analyses were assessed as directly applicable with potentially serious limitations.
- One cost-utility analysis found that for treating aortic stenosis:
    - In inoperable patients TAVI was cost effective compared to standard therapy at a threshold of £30,000 (ICER: £29,506 per QALY gained)
    - In high operative risk patients surgical aortic valve implantation dominated TAVI.

  The analysis was assessed as partially applicable with potentially serious limitations.

- One cost-utility analysis found that for treating aortic stenosis:
    - In inoperable patients TAVI was cost effective compared to medical therapy at a threshold of £30,000 (ICER: £26,673 per QALY gained)
    - In intermediate operative risk patients TAVI was not cost effective compared to surgical aortic valve implantation (ICER: £51,210 per QALY gained).

  The analysis was assessed as partially applicable with potentially serious limitations.

- One cost-utility analysis found that for treating aortic stenosis:
    - In high operative risk patients TAVI was cost effective compared to surgical aortic valve implantation (ICER: £9,510 per QALY gained)
    - In intermediate operative risk patients TAVI was cost effective compared to surgical aortic valve implantation (ICER: £15,553 per QALY gained).

  The analysis was assessed as partially applicable with potentially serious limitations

- One cost-utility analysis found that TAVI dominated surgical aortic valve implantation for treating aortic stenosis in an intermediate operative risk population. The analysis was assessed as partially applicable with potentially serious limitations.
- Another cost-utility analysis found that TAVI was cost-effective compared to surgical aortic valve implantation at a threshold of £30,000 for treating aortic stenosis in an intermediate operative risk population (ICER: £25,856 per QALY gained). The analysis was assessed as partially applicable with potentially serious limitations
- Another cost-utility analysis found that TAVI was not cost-effective compared to surgical aortic valve implantation for treating aortic stenosis in an intermediate operative risk

population (ICER: £43,055 per QALY gained). The analysis was assessed as partially applicable with potentially serious limitations

- One cost-utility analysis found that balloon expandable TAVI was cost effective compared to surgical aortic valve implantation for treating aortic stenosis in a low operative risk population (ICER: £15,900 per QALY gained). The analysis was assessed to be partially applicable with potentially serious limitations
- One cost-utility analysis found that mini-sternotomy was dominated by full median sternotomy for treating aortic valve disease. The analysis was assessed to be directly applicable with potentially serious limitations.
- Two cost-utility analyses found that percutaneous mitral valve repair was cost effective compared to medical management at a threshold of £30,000 for treating primary and secondary mitral regurgitation in an inoperable population (ICERs: £22,153 per QALY gained and £13,549 per QALY gained respectively). The analyses were assessed as directly applicable and partially applicable with potentially serious limitations.
- One cost-utility analysis found that percutaneous mitral valve repair was not cost effective compared with medical management for treating a secondary mitral regurgitation in an inoperable population (ICER: 30,057 per QALY gained). The analysis was assessed as directly applicable with minor limitations.
- One cost-comparison analysis found that minimally invasive surgery costed £411 less per person for treating mixed mitral disease. The analysis was assessed as partially applicable with potentially serious limitations.
- One original cost-utility analysis found that for treating aortic stenosis:
    - In intermediate operative risk patients TAVI is not cost effective compared to surgical aortic valve implantation (ICER: £129,343 per QALY gained)
    - In high operative risk patients TAVI is not cost effective compared to surgical aortic valve implantation (ICER: £92,945 per QALY gained)

  The analysis was assessed as directly applicable with minor limitations

- One original cost-utility analysis found that percutaneous edge-to-edge repair with MitraClip device is not cost effective compared to medical management at a £30,000 threshold in an inoperable population (ICER: £30,283per QALY gained). The analysis was assessed as directly applicable with minor limitations.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Outcomes considered to be critical as listed in the protocol were all-cause mortality at ≥12 months, cardiac mortality at ≥12 months, intervention-related mortality at 30 days, onset or exacerbation of heart failure at ≥12 months, intervention-related stroke or TIA at 30 days, intervention-related major bleeding at 30 days and need for re-intervention at ≥12 months.

Outcomes listed as important in the protocol were length of stay (following initial intervention), re-hospitalisation at ≥12 months, intervention-related pacemaker implantation at 30 days, intervention-related atrial fibrillation at 30 days, intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication) and prosthetic valve endocarditis at ≥12 months.

Renal failure and myocardial infarction were discussed as additional outcomes relevant to this review, however due to the large number of outcomes already included, the GC agreed that these two outcomes were less important to consider than those listed above. It was agreed that renal failure would still be considered in terms of any health economic modelling that will be performed due to the costs that can be associated with renal failure, but that

myocardial infarction did not need to be included in the protocol as the costs associated with renal failure were considered to be higher and more important to capture than those of myocardial infarction.

All listed outcomes were reported when all of the strata and comparisons are considered together, however, for certain strata and comparisons the number of outcomes reported was limited. Overall, the studies covering aortic valve disease covered more of the outcomes listed in the protocol, whereas studies included in the various mitral valve disease strata reported fewer outcomes.

1.7.1.2 The quality of the evidence

No relevant RCTs were identified for the following populations: aortic stenosis (bicuspid) and aortic regurgitation.

Fourty-three RCTs were included in this review, covering various comparisons for different types of heart valve disease as detailed below.

Aortic valve disease

Aortic stenosis (non-bicuspid):

- Minimally invasive surgery replacement vs. standard surgery replacement (n=1 study)
- Transcatheter replacement vs. standard surgery replacement (n=7 studies)
- Transcatheter replacement vs. pharmacological management (n=1 study)
- Transcatheter replacement vs. surgical replacement (unclear/mixed invasiveness, n=1 study)

Aortic stenosis (mixed bicuspid and non-bicuspid or unclear):

- Minimally invasive surgery replacement vs. standard surgery replacement (n=5 studies)

Mixed/unclear aortic valve disease:

- Minimally invasive surgery replacement vs. standard surgery replacement (n=7 studies)

Mitral valve disease

Mitral stenosis:

- Minimally invasive surgery repair vs. standard surgery repair (n=1 study)
- Transcatheter repair vs. standard surgery repair (n=2 studies)
- Transcatheter repair vs. minimally invasive surgery repair (n=5 studies)
- Transcatheter repair vs. surgery repair (mixed invasiveness, n=1 study)

Mitral regurgitation:

- Standard surgery replacement vs. standard surgery repair (n=1 study)

- Minimally invasive surgery repair vs. standard surgery repair (n=1 study)
- Minimally invasive surgery (mixed repair/replacement) vs. standard surgery (mixed repair/replacement, n=1 study)
- Surgical replacement (unclear invasiveness) vs. surgical repair (unclear invasiveness, n=1 study)
- Transcatheter repair vs. pharmacological management (n=3 studies)
- Transcatheter repair vs. surgery (mixed repair/replacement and unclear invasiveness, n=1 study)

Unclear/mixed mitral valve disease:

- Minimally invasive surgery replacement vs. standard surgery replacement (n=3 studies)

Evidence ranged from high to very low quality, with the majority of the evidence being of low or very low quality, primarily due to risk of bias and imprecision. Population and/or intervention indirectness was also a reason for downgrading the quality of some of the evidence as they did not match the specific groups described in the protocol. For example, studies where the population was mixed (i.e. some had aortic stenosis and some had aortic regurgitation, with no 75% majority within the study) were downgraded for indirectness. Similarly, studies where the type of intervention being received was mixed (i.e. some receiving repair and some receiving replacement procedures) or unclear (e.g. the invasiveness of the surgery was not specified) were also downgraded for indirectness. Additionally, some studies only reported short-term data (e.g. in-hospital) for outcomes the committee were interested in at longer follow-up times (such as mortality and re-intervention), which was also a reason for downgrading for the relevant outcomes.

Despite the number of included studies, the overall evidence for each comparison and type of heart valve disease was limited in most cases, with only one relatively small included study for the majority of the reported comparisons across aortic and mitral valve disease strata. However, in terms of the number of included studies and total number of participants, the evidence base was stronger in particular for the comparison between transcatheter replacement and standard surgery (median sternotomy) replacement in the aortic stenosis (non-bicuspid) stratum, though most outcomes were graded low or very low quality as with other strata.

In terms of the comparisons between TAVI and surgical intervention for non-bicuspid aortic stenosis, the committee agreed that were was a lack of long-term evidence as follow-up was only up to 5 years for most outcomes and much longer term data would improve the comparison of outcomes between these two interventions.

1.7.13 Benefits and harms

Aortic stenosis (non-bicuspid):

<u>Transcatheter replacement:</u>

- When compared with standard surgery replacement across seven RCTs, both benefits and harms of transcatheter replacement were identified in those with non-bicuspid aortic stenosis at various operative risks (low, intermediate or high). Three

studies focused on low operative risk patients, two studies on intermediate operative risk patients and two studies on high operative risk patients. Clinically important benefits were identified for the following outcomes: cardiac mortality at ≥12 months (studies reporting time-to-event data), mortality at 30 days, major bleeding, length of stay and atrial fibrillation. However, the following clinically important harms of transcatheter replacement were also identified: all-cause mortality at ≥12 months (time-to-event and dichotomous data), cardiac mortality at ≥12 months (studies reporting only dichotomous data), re-hospitalisation (studies reporting only dichotomous data),pacemaker implantation and major vascular complications. Results for quality of life, stroke or TIA, need for re-intervention, re-hospitalisation based on time-to-event data and prosthetic valve endocarditis suggested no clinically important difference between transcatheter replacement and standard surgery replacement. There was uncertainty in the direction of the effect for all outcomes apart from major bleeding, need for re-intervention, re-hospitalisation (studies reporting only dichotomous data), pacemaker implantation, atrial fibrillation and major vascular complications. However, uncertainty was still present for these outcomes in terms of the size of the effect, meaning for those where the absolute effect suggested a clinically important difference between groups there was uncertainty about whether the true difference was clinically important.

- One additional study compared transcatheter replacement with surgical replacement (the invasiveness of the surgery in this study was unclear). As with the seven studies mentioned in the section above, this study also suggested clinically important benefits of transcatheter replacement in terms of mortality at 30 days, major bleeding and atrial fibrillation, and a harm in terms of pacemaker implantation, when compared to surgical replacement. However, it also suggested a benefit in terms of cardiac mortality at ≥12 months, which the seven RCTs in the section above suggested was a harm of transcatheter intervention. The results of this study suggested no clinically important difference between transcatheter replacement and surgical replacement (unclear invasiveness) for the following outcomes: all-cause mortality at ≥12 months, quality of life, onset or exacerbation of heart failure, stroke or TIA, need for re-intervention, major vascular complications and prosthetic valve endocarditis. There was uncertainty in the direction of the effect for all outcomes apart from onset or exacerbation of heart failure, major bleeding, pacemaker implantation and atrial fibrillation. However, uncertainty was still present for the major bleeding outcome in terms of the size of the effect, meaning there was uncertainty about whether the true difference was clinically important.

Although no major differences were observed between TAVI and standard surgery replacement across the seven included RCTs for most of the outcomes that were reported, the health economic model (see discussion below) demonstrated that TAVI was not cost-effective in patients where surgery was an alternative, regardless of the operative risk (intermediate or high) and the age group. The committee therefore agreed that, based on the clinical and cost-effectiveness evidence combined, surgery should be offered to patients that require intervention for aortic stenosis. Despite all of the evidence being from the non-bicuspid aortic stenosis population, the recommendation was also extrapolated to the bicuspid aortic stenosis population as it was agreed that the type of aortic stenosis (bicuspid or non-bicuspid) would not change the fact that surgery is a suitable procedure for aortic stenosis requiring intervention. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning surgery would usually be the choice in this population currently.

- In one study that compared transcatheter replacement with pharmacological management in those where surgical intervention is not suitable, benefits and harms of transcatheter replacement were identified. Clinically important benefits were reported for the following outcomes: all-cause mortality at ≥12 months, cardiac mortality at ≥12 months, need for reintervention and rehospitalisation. For all of these

outcomes, confidence intervals were also consistent with a clinically important benefit and there was no uncertainty about this conclusion. However, clinically important harms associated with transcatheter replacement were mortality at 30 days, stroke or TIA, major bleeding and major vascular complications. There was uncertainty in the direction of the effect for the outcome of mortality at 30 days and uncertainty in terms of the size of the effect was present for stroke or TIA, major bleeding and major vascular complications, meaning there was uncertainty about whether the true difference for these outcomes was clinically important. Results reported for pacemaker implantation, atrial fibrillation and valve endocarditis suggested no clinically important difference between transcatheter replacement and pharmacological management in those where surgery is not suitable, though there was uncertainty in this conclusion for endocarditis based on the confidence intervals as the upper confidence interval was consistent with a harm of the transcatheter procedure.

The committee agreed that given TAVI is the only option for intervention for those with inoperable aortic stenosis, because pharmacological management is not sufficient to help symptoms in severe aortic stenosis and severe aortic stenosis can be fatal in some cases when left without intervention, as well as because the evidence from one study highlighted benefits of TAVI in terms of all-cause mortality, cardiac mortality, need for reintervention and rehospitalisation, it should be offered as an option for this population. Although clinical data was only available from a single study, with all outcomes being graded low-very low quality, an offer recommendation was made as it was agreed that it was the only option for those with inoperable aortic stenosis and the option of an intervention should be provided, even if not all patients wish to have the procedure. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated and this area was not prioritised for a research recommendation for the same reasons.

The committee agreed that a cross referral to the NICE interventional procedure guidance (IPG586) on transcatheter aortic valve implantation for aortic stenosis was relevant.

<u>Invasiveness of surgery:</u>

- Evidence from one study comparing minimally invasive surgery replacement with standard surgery replacement suggested more harms than benefits of minimally invasive replacement. Clinically important harms associated with the minimally invasive procedure were all-cause mortality at ≥12 months, mortality at 30 days and prosthetic valve endocarditis. However, there was uncertainty in the direction of the effect for all three of these outcomes based on the confidence intervals, meaning there was uncertainty about whether the true difference was clinically important. The only clinically important benefit identified for minimally invasive replacement was atrial fibrillation development. For this outcome, confidence intervals were also consistent with a clinically important benefit and there was no uncertainty about this conclusion. In addition, no clinically important difference was reported for the following outcomes: stroke or TIA, major bleeding, need for re-intervention and pacemaker implantation; however, there was uncertainty in this conclusion for all outcomes based on the confidence intervals as the upper confidence interval was consistent with a harm of the transcatheter procedure for stroke or TIA, major bleeding and need for re-intervention, and the lower and upper confidence intervals for pacemaker implantation were consistent with a benefit or harm of the transcatheter procedure, respectively.

- Fewer outcomes were reported for this particular comparison relative to the other comparisons mentioned for this stratum.

See concluding paragraphs under 'mixed/unclear aortic valve disease' section below for information about how the above evidence contributed to the recommendations.

Aortic stenosis (mixed bicuspid and non-bicuspid or unclear)

This stratum includes studies where it was unclear whether bicuspid valve disease was excluded from the study population and was included as indirect evidence, as the protocol had initially stratified by bicuspid and non-bicuspid aortic stenosis from the outset. Five studies were included within this stratum and all compared minimally invasive surgery replacement with standard surgery replacement.

- Based on absolute effects, a clinically important benefit in terms of mortality at 30 days was identified for minimally invasive surgery replacement; however clinically important harms were identified for all-cause mortality at ≥12 months and cardiac mortality at ≥12 months. For all three of these outcomes, there was uncertainty in the direction of the effect based on confidence intervals, meaning there was uncertainty about whether the true difference represented a clinically important harm or benefit of minimally invasive replacement. No clinically important difference was reported for the following additional outcomes: quality of life, stroke or TIA, major bleeding, need for re-intervention, length of hospital or intensive care unit stay, pacemaker implantation, atrial fibrillation and prosthetic valve endocarditis; however, based on the confidence intervals, there was uncertainty in this conclusion for all outcomes other than need for re-intervention and length of hospital stay intervals as confidence intervals were consistent with a harm or benefit (or both in some cases) of minimally invasive surgery replacement.

See concluding paragraphs under 'mixed/unclear aortic valve disease' section below for information about how the above evidence contributed to the recommendations.

Mixed/unclear aortic valve disease

This stratum includes studies where the type of aortic valve disease included was unclear or the population was mixed, with no 75% majority (i.e. some people had aortic stenosis and some had aortic regurgitation) and was included as indirect evidence, as the protocol had initially stratified by the two types of aortic valve disease from the outset. Seven studies were included within this stratum and all compared minimally invasive surgery replacement with standard surgery replacement.

- Clinically important benefits in terms of quality of life, major bleeding, length of hospital stay and atrial fibrillation were identified for minimally invasive surgery replacement; however, clinically important harms were identified for all-cause mortality at ≥12 months, cardiac mortality at ≥12 months and pacemaker implantation. For all of these outcomes there was uncertainty in the direction or size of the effect based on confidence intervals, meaning there was uncertainty about whether the true difference was clinically important and for some outcomes whether a clinically important harm rather than benefit, or vice versa, was present. No clinically important difference was reported for the following additional outcomes: mortality at 30 days, stroke or TIA , need for re-intervention and length of intensive care unit stay; however, based on the confidence intervals, there was uncertainty in this conclusion for all outcomes other than length of intensive care unit stay as confidence intervals were consistent with a harm or benefit (or both in the case of mortality at 30 days) of minimally invasive surgery replacement.

Evidence from 14 RCTs comparing minimally invasive surgery replacement with standard surgery replacement by median sternotomy across different aortic valve disease populations informed the recommendation on the invasiveness of surgery in aortic valve disease. There was 1 study covering non-bicuspid aortic stenosis, 5 studies covering aortic stenosis where it was unclear whether bicuspid disease was excluded and 7 studies covering populations where some patients had aortic stenosis and some patients had aortic regurgitation or the population was only described as aortic valve disease, representing a general aortic valve disease population rather than focussing specifically on stenosis or regurgitation.

Despite some clinically important harms of minimally invasive surgery being identified across the included studies, and a health economic study that suggested minimally invasive surgery was not cost-effective compared with median sternotomy replacement, it was noted that all RCTs were small and for many outcomes only a small number of events were observed. The health economic study was also limited for the same reasons, as it was based on one of the RCTs included in the clinical evidence. It was also limited to a 12 month time-horizon, which may be too short to draw conclusions about cost effectiveness over a lifetime, though the committee agreed it is likely there would not be a large difference in outcomes after 12 months. In addition, the committee agreed that in their clinical experience there was no difference between minimally invasive and standard surgery replacement in terms of outcomes when performed by those with expertise in minimally invasive surgery, which could be supported by a large amount of non-randomised evidence not included in this review of RCTs.

It was agreed that the evidence included was insufficient to limit the use of minimally invasive surgery and a decision was made to offer either in those undergoing surgical replacement of the aortic valve, with the decision to be based on patient characteristics and preferences. For example, median sternotomy may be more appropriate if a patient requires concomitant procedures such as other valve or coronary interventions at the same time as the aortic valve operation. It was noted that a lack of expertise in minimally invasive surgery locally should not be used as a reason for not performing a minimally invasive procedure and patients should be referred to a centre where there is expertise if this procedure is deemed most suitable for the patient.

Though no or limited evidence was included for bicuspid aortic stenosis, aortic regurgitation (bicuspid or non-bicuspid) and those with mixed aortic valve disease (aortic stenosis and regurgitation in same patient), the recommendation on the invasiveness of surgery was applied to all aortic valve disease, as the type of aortic valve disease does not affect decisions about the invasiveness of surgery and evidence can therefore be extrapolated to these populations.

Mitral stenosis

<u>Transcatheter repair:</u>

- Two studies compared transcatheter repair with standard surgery repair in those with rheumatic mitral stenosis. No clinically important benefits of transcatheter repair over standard surgery repair were identified. Although the absolute effect demonstrated clinically important harms associated with transcatheter repair (all-cause mortality and cardiac mortality at ≥12 months), this was based on a very small number of events with 1 event in the transcatheter arm and 0 events in the surgery arm and there was uncertainty in the direction of the effect based on confidence intervals – there is therefore insufficient evidence to conclude there is a harm of transcatheter repair for these outcomes. Results also indicated no clinically important difference for mortality at 30 days, stroke or TIA, need for re-intervention and atrial fibrillation based on

absolute effects; however, based on the confidence intervals, there was uncertainty in this conclusion for all outcomes as confidence intervals were consistent with a harm or benefit (or both for all apart from need for re-intervention) of transcatheter repair. Only six of the fourteen outcomes listed in the protocol were reported across the studies.

- Five studies compared transcatheter repair with minimally invasive surgery repair in those with rheumatic mitral stenosis. As above when compared to standard surgery repair, no clinically important benefits of transcatheter repair over minimally invasive surgery repair were identified. For this comparison, the only clinically important harm associated with transcatheter repair was major vascular complications; however, based on confidence intervals there was uncertainty in the size of the effect, meaning there was uncertainty about whether the true difference was clinically important. No clinically important difference was reported for the following outcomes: all-cause mortality ≥12 months, cardiac mortality at ≥12 months, mortality at 30 days, stroke or TIA, major bleeding and need for re-intervention; however, based on the confidence intervals, there was uncertainty in this conclusion for the three mortality outcomes and need for re-intervention as upper and lower confidence intervals were consistent with a harm or benefit of transcatheter repair, respectively, in all three cases. Only seven of the fourteen outcomes listed in the protocol were reported across the studies.

- An additional study compared transcatheter repair with surgical repair (where the invasiveness of the surgery was different for different patients) in those with rheumatic mitral stenosis. For this comparison, clinically important benefits of transcatheter repair were identified in terms of major bleeding, pacemaker implantation and atrial fibrillation. Major vascular complications was identified as a clinically important harm associated with transcatheter repair. However, this was based on a single study with a small population, and the difference between arms in terms of number of events was between 2 and 6 for each of these outcomes. In addition, for all of the above outcomes, there was uncertainty in the size of the effect as the lower confidence interval was consistent with no clinically important difference, meaning there was uncertainty about whether the true difference was clinically important. No clinically important difference between transcatheter repair and surgical repair was identified for all-cause mortality ≥12 months, cardiac mortality at ≥12 months, mortality at 30 days and need for re-intervention; however, based on the confidence intervals, there was uncertainty in this conclusion for all outcomes as upper and lower confidence intervals were consistent with a harm or benefit of transcatheter repair, respectively, in all cases. Only eight of the fourteen outcomes listed in the protocol were reported within the study.

Although the evidence discussed above demonstrates few clinically important differences between transcatheter valvotomy and surgical valvotomy for rheumatic mitral stenosis, a decision based on committee experience and current practice was made to recommend the transcatheter procedure over the surgical procedure, as it was agreed that surgical valvotomy is no longer commonly used in practice as it is established that similar results can be achieved with the transcatheter procedure with less trauma and scarring. The strength of the recommendation was consider rather than offer based on limitations with the included evidence, including small studies with only a small number of events in many cases, as well as the majority of outcomes being graded very low quality.

A further recommendation was made to offer mitral valve replacement in those with rheumatic mitral stenosis requiring an intervention where transcatheter valvotomy would not be suitable. This recommendation was made based on current practice as no evidence was included in the review to support this, but it was agreed this was an important recommendation to make to cover patients where the transcatheter valvotomy procedure would not be an option but where intervention is required. Despite there being no evidence

for this, the committee noted that as this is a population who are considered to need intervention, replacement is the only alternative where transcatheter valvotomy is not suitable and it would therefore be current practice to offer valve replacement in these circumstances. As they have been deemed to need intervention then it would be unethical to withhold this if suitable for the procedure, possibly explaining the lack of studies comparing replacement with no treatment in this population. One example of where a transcatheter valvotomy is contraindicated in current practice is where there is co-existent mitral regurgitation. The degree of calcification that has developed may also affect whether or not transcatheter valvotomy is a suitable procedure.

It was agreed that it would not be appropriate to extrapolate evidence from the rheumatic mitral stenosis population to the calcific degenerative mitral stenosis population as they are two very different pathologies. Rheumatic mitral stenosis occurs as a result of rheumatic fever, whereas calcific degenerative mitral stenosis occurs due to calcific degeneration. The onset of rheumatic mitral stenosis is usually at a younger age than that of calcific degenerative mitral stenosis. It was noted that although some patients with rheumatic stenosis may present with some calcification of the rheumatic valve as they age, the valve disease is still considered to be rheumatic and is different to calcific degenerative mitral stenosis where calcification of the valve is the main driver of the valve disease. As there was no evidence included to cover calcific degenerative mitral stenosis in the review, a research recommendation covering the management of this population was therefore agreed (see Appendix J.1.1 for details).

Invasiveness of surgery:

- One study compared minimally invasive surgery repair with standard surgery repair in those with rheumatic mitral stenosis. No clinically important benefits of minimally invasive surgery repair were identified when compared to standard surgery repair and a clinically important harm was reported in terms of need for re-intervention. There was no uncertainty in this conclusion for need for re-intervention as the confidence interval was also consistent with a clinically important harm. No clinically important difference was reported for all-cause mortality at ≥12 months, cardiac mortality at ≥12 months, mortality at 30 days and stroke or TIA; however, based on the confidence intervals, there was uncertainty in this conclusion for all outcomes as upper and lower confidence intervals were consistent with a harm or benefit of minimally invasive surgery repair, respectively, in all cases. Only five of the fourteen outcomes listed in the protocol were reported within the study.

As it was agreed that surgical valvotomy is no longer commonly used in UK practice, with the transcatheter valvotomy procedure being performed where suitable and replacement where this was not possible, surgical repair was not included in the recommendations because it is very rarely performed currently in rheumatic mitral valve disease and this evidence on minimally invasive vs. standard surgery repair was therefore not used to inform any of the recommendations. Research recommendations were also not made in this area for the same reasons.

Mitral regurgitation

Replacement or repair

- One study compared standard surgery replacement with standard surgery repair in those with mitral regurgitation of various aetiologies (including myxamatous, rheumatic, ischaemic or due to endocarditis). Although clinically important benefits of

replacement in terms of in-hospital all-cause mortality, in-hospital cardiac mortality and in-hospital need for re-intervention were identified based on the absolute effect, for all three outcomes this was based on differences of only 1-2 events between the arms in a single, small study and there was uncertainty in the direction of the effect for these outcomes as confidence intervals indicated that the true effect could also be a clinically important harm of standard surgery replacement compared to repair. In addition, no long-term follow-up data was available for these outcomes. No clinically important harms were identified. No clinically important difference was reported for stroke or TIA between the two groups; however, based on the confidence intervals, there was uncertainty in this conclusion as the upper confidence interval was consistent with a harm of replacement for this outcome. Only four of the fourteen outcomes listed in the protocol were reported within the study.

- Two studies compared surgical replacement (unclear invasiveness) with surgical repair (unclear invasiveness) in those with secondary mitral regurgitation. Clinically important benefits of replacement identified were quality of life measured on the Minnesota Living with Heart Failure questionnaire and the need for re-intervention; however, there was uncertainty in the size of the effect for both outcomes, meaning there was uncertainty about whether the true difference was clinically important. Clinically important harms associated with replacement over repair were all-cause mortality at ≥12 months, cardiac mortality at ≥12 months and mortality at 30 days, though there was uncertainty in the direction of the effect for these outcomes as confidence intervals indicated that the true effect could also be a clinically important benefit of surgical replacement compared to surgical repair. No clinically important difference was reported for the following outcomes: quality of life measured on EQ-5D and SF-12 questionnaires, onset or exacerbation of heart failure, stroke or TIA, major bleeding, length of stay, pacemaker implantation, major vascular complications and valve endocarditis; however, based on the confidence intervals, there was uncertainty in this conclusion for all outcomes apart from valve endocarditis as confidence intervals were consistent with a harm or benefit (or both for some outcomes) of surgical replacement. These results were based on two small studies and in most cases a small number of events, with uncertainty present based on confidence intervals, even for those outcomes where a harm or benefit was suggested by the absolute effect. The strongest effect observed was for need for re-intervention at 24 months, where fewer events occurred in the replacement group.

Evidence from the included studies was limited based on the small number of participants included in each trial, a substantial amount of uncertainty in the direction of effect for most outcomes and the small number of events reported for the majority of outcomes. In addition, most outcomes were graded very low quality. It was highlighted that the lack of stronger evidence may be due to the fact that surgical repair has been the preferred option in recent decades due to strong non-randomised evidence and that randomising patients to repair or replacement was not considered ethical. Therefore, based on the limitations of the included evidence, recommendations in line with current practice were made, with surgical mitral valve repair recommended where repair was suitable and surgical mitral valve replacement recommended where repair was not possible. Based on evidence discussed in the following section under 'invasiveness of surgery', the recommendations specified this should be by minimally invasive surgery or median sternotomy, with the decision based on patient characteristics and preferences.

The committee noted that there are differences in the aetiology and treatment of primary and secondary mitral regurgitation in practice. Primary mitral regurgitation is a result of degeneration of the valve components whereas secondary mitral regurgitation develops as a result of underlying enlargement of cardiac chambers (left ventricle or left atrium) rather than valve degeneration. In those with primary mitral regurgitation and an indication for intervention, it is established that valve intervention should be performed to for those suitable for intervention, as remaining on conservative management would lead to deterioration of

condition. For this reason, offer recommendations were made for primary mitral regurgitation where intervention is required. However, those with secondary mitral regurgitation requiring intervention are usually treated for their underlying cause (heart failure or atrial fibrillation) initially, with a decision about whether a valve intervention is also required or appropriate following this. For this reason, recommendations in secondary mitral regurgitation were consider recommendations. The different strength of recommendations for primary and secondary mitral regurgitation for those where intervention is required were used to capture the difference in aetiology and current practice, as intervention for the mitral regurgitation may not always be required in secondary mitral regurgitation as treating the underlying cause may mean that the mitral regurgitation is improved or resolved and no longer needs intervention, while primary mitral regurgitation is caused by degenerated valves and therefore the heart valve itself needs to be treated as there is no other underlying cause that could be treated instead.

Invasiveness of surgery

- One study compared minimally invasive surgery repair with median sternotomy repair in those with mitral regurgitation due to Barlow disease. A clinically important benefit was identified in terms of length of stay in the minimally invasive group, though there was some uncertainty in the size of this effect, and no clinically important harms of minimally invasive surgery repair were identified. No clinically important difference was reported for the following outcomes: all-cause mortality at ≥12 months, intra/postoperative mortality, quality of life on the SF-36 questionnaire, stroke or TIA, major bleeding, need for re-intervention and valve endocarditis; however, based on the confidence intervals, there was uncertainty in this conclusion for all outcomes apart from the social activities domain on the SF-36 questionnaire and valve endocarditis as confidence intervals were consistent with a harm or benefit of minimally invasive surgery repair compared to median sternotomy repair. Only eight of the fourteen outcomes listed in the protocol were reported within the study.

- One study compared minimally invasive surgery (mixed repair and replacement) with median sternotomy (mixed repair and replacement) in those with mitral regurgitation of unclear aetiology. Although clinically important benefits of minimally invasive surgery were identified in terms of major bleeding and pacemaker implantation based on the absolute effects, there was only 1 event in the standard surgery arm and 0 events in the minimally invasive surgery arm of a single study with only 40 participants. The confidence intervals indicated uncertainty in the direction of the effect and that the true effect could also be a clinically important harm of minimally invasive surgery compared to median sternotomy. No clinically important harms of minimally invasive surgery were identified. No clinically important difference was reported for the following outcomes, though no long-term follow-up data was available for the mortality outcomes: in-hospital all-cause mortality, in hospital cardiac mortality, onset/exacerbation of heart failure postoperatively and stroke or TIA; however, based on the confidence intervals, there was uncertainty in this conclusion for all outcomes as confidence intervals were consistent with a harm (or both a benefit and harm for the mortality outcomes) of minimally invasive surgery compared to median sternotomy. Only six of the fourteen outcomes listed in the protocol were reported within the study.

Overall, although some clinically important differences were observed, suggesting benefits of minimally invasive procedures in terms of length of stay and reduced cost per person compared to median sternotomy procedures, limitations of the included studies, including small participant numbers and a small number of events for many reported outcomes, a lack of long-term data for many outcomes and most outcomes being graded low-very low quality, meant there was insufficient evidence to recommend one over the other. Therefore, it was

agreed that recommendations, which were consider or offer based on the specific type of procedure being recommended (for example, repair or replacement) or type of mitral regurgitation specified (primary or secondary), should include minimally invasive and standard surgery as options for those with mitral regurgitation requiring mitral valve surgery was made, with the decision being based on patient characteristics and preferences. For example, median sternotomy may be more appropriate if a patient requires concomitant procedures such as other valve or coronary interventions at the same time as the mitral valve operation. It was noted that lack of expertise in minimally invasive surgery locally should not be used as a reason for not performing a minimally invasive procedure and patients should be referred to a centre where there is expertise if this procedure is deemed most suitable for the patient. It was also noted that observational evidence suggests higher likelihood of successful mitral valve repair rather than replacement when median sternotomy rather than minimally invasive surgery approach is used, particularly for complex mitral valve morphology

Transcatheter repair

- Three studies compared transcatheter repair with pharmacological management in those with secondary mitral regurgitation. Clinically important benefits associated with transcatheter repair were all-cause mortality at ≥12 months, cardiac mortality at ≥12 months, quality of life on the EQ-5D, KCCQ and SF-36 physical questionnaires (note no difference was reported for the SF-36 mental component questionnaire), onset/exacerbation of heart failure and rehospitalisation. However, there was heterogeneity in the results for all-cause mortality, cardiac mortality and onset/exacerbation of heart failure between the studies as some suggested a benefit while others suggested a harm or no difference for all three outcomes. In addition, for all of these outcomes there was uncertainty in the direction or size of the effect based on confidence intervals, meaning there was uncertainty about whether the true difference was clinically important or, for mortality and re-hospitalisation outcomes, whether there was actually a clinically important harm of transcatheter repair rather than benefit. Though a clinically important harm of transcatheter repair was identified for mortality at 30 days based on the absolute effect, there was a difference of only 3 events between the two study arms across the 2 studies reporting this outcome and the confidence intervals demonstrated uncertainty in the direction of the effect, meaning the true effect could also be a clinically important benefit of transcatheter repair for this outcome. No clinically important difference was reported for the following outcomes: stroke or TIA, major bleeding, need for intervention, major vascular complications and prosthetic valve endocarditis; however, based on the confidence intervals, there was uncertainty in this conclusion for major bleeding, major vascular complications and prosthetic valve endocarditis as the upper confidence interval was consistent with a harm of transcatheter repair.

Two studies were specifically in a population where surgery was not suitable, while the operative risk of the third study was unclear. Health economic modelling performed as part of the guideline focused specifically on secondary mitral regurgitation when surgery is not suitable. The included evidence highlighted uncertainty in the direction of the effect for some outcomes in secondary mitral regurgitation, and this uncertainty was still present even between the two studies focusing on the population where surgery was not suitable. Very few outcomes were reported by all of the included studies, with some reported outcomes only covered by a single study. There was uncertainty in the direction of the 3 outcomes, including all-cause mortality, cardiac mortality and onset/exacerbation of heart failure at 1-2 years.

The differences in the results obtained from 2 clinical studies included that covered the inoperable population are possibly explained by the fact that patients from the trial where benefits were not observed (MITRA-FR) were considered to have more advanced heart failure and less severe mitral regurgitation, with a larger proportion having moderate rather than severe mitral regurgitation, than those in the other trial (COAPT). The type of transcatheter procedure used in these two studies was transcatheter mitral edge-to-edge repair. Despite some clinical evidence of benefits of transcatheter intervention over pharmacological treatment in one of these studies, the health economic model that was developed as part of the guideline demonstrated that at its current list price, this procedure was not cost-effective for the secondary mitral regurgitation population where surgery is unsuitable. Therefore, it was recommended that medical management is offered in preference to transcatheter mitral edge-to-edge repair for adults with heart failure and severe secondary mitral regurgitation, if surgery is unsuitable.

- One study compared transcatheter repair with surgery (mixed repair and replacement, unclear invasiveness) in a population that had some patients with primary disease and some with secondary disease. The clinically important benefits identified for transcatheter repair were all-cause mortality at ≥12 months and mortality at 30 days. However, there was uncertainty present for both of these outcomes in terms of the direction of the effect based on confidence intervals. The largest difference observed between the groups was a clinically important harm of transcatheter repair in terms of need for re-intervention; however, uncertainty based on the confidence interval was present as the lower confidence interval was consistent with there being no clinically important difference. In addition, no clinically important difference was reported for the following outcomes: quality of life as measured by the SF-36 questionnaire for physical and mental components, stroke or TIA, atrial fibrillation and major vascular complications; however, there was uncertainty in this conclusion for the SF-36 quality of life outcomes and stroke or TIA, as the confidence intervals were consistent with a clinically important benefit or harm, or both for the SF-36 physical component outcome. Only seven of the fourteen outcomes listed in the protocol were reported within the study.

  No clinical evidence was identified comparing transcatheter mitral valve repair with medical management in those with primary mitral regurgitation where surgery is not suitable. However, it was noted that the lack of evidence in this area may be because it is well established that medical management in those with primary mitral regurgitation that need intervention does not improve the outcomes of patients and therefore transcatheter mitral valve repair would be useful in patients where surgery cannot be performed. One health economic study based on a non-randomised EVEREST II high risk registry found that transcatheter repair was cost effective over medical management in those not eligible for surgery with severe mitral regurgitation. This was from a UK NHS perspective; however, it was not limited to primary mitral regurgitation as it also included patients with secondary mitral regurgitation. It was also considered to have potentially serious limitations due to its design, as data was obtained from a prospective, single arm registry with a control group that was obtained retrospectively. Therefore, a consider recommendation for transcatheter mitral valve repair in primary mitral regurgitation where surgery was not suitable was made. A research recommendation was not made despite the absence of clinical evidence for this population as it was not prioritised due to it being established that medical management alone in those with primary mitral regurgitation that need intervention does not improve outcomes.

Mixed/unclear mitral valve disease

This stratum includes studies where the type of mitral valve disease included was unclear or the population was mixed, with no 75% majority (i.e. some people had mitral stenosis and some had mitral regurgitation) and was included as indirect evidence, as the protocol had initially stratified by the two types of mitral valve disease from the outset. Three studies were included within this stratum and all compared minimally invasive surgery replacement with standard surgery replacement.

- Clinically important benefits of minimally invasive surgery replacement were identified in terms of in-hospital/postoperative need for re-intervention and length of hospital stay; however, there was uncertainty in the size of this effect based on confidence intervals, meaning there was uncertainty as to whether the true difference was clinically important. Though a clinically important benefit was also identified for in-hospital/postoperative all-cause mortality based on the absolute effect, this was driven by a single study as two other included studies demonstrated no difference between the groups. In addition, no long-term follow-up data was available for the mortality and need for re-intervention outcomes. No clinically important harms of minimally invasive surgery replacement were identified when compared to standard surgery replacement and no clinically important difference was reported for in-hospital/postoperative cardiac mortality, stroke or TIA and prosthetic valve endocarditis; however, there was uncertainty in this conclusion for all three of these outcomes as the upper confidence intervals were consistent with a clinically important harm of minimally invasive surgery replacement, or for cardiac mortality the upper and lower confidence intervals suggested a clinically important harm or benefit, respectively. Despite more benefits than harms being identified, only six of the fourteen outcomes listed in the protocol were reported by these studies and long-term follow-up data was missing for the mortality and re-intervention outcomes. All outcomes were also graded very low quality.

Evidence from these studies contributed to the decision to include minimally invasive and standard surgery as options for those requiring surgery for mitral regurgitation, as the type of mitral valve disease does not usually affect decisions about the invasiveness of surgery in current practice and this was included as indirect evidence. Limitations with this evidence and a lack of strong differences between the groups meant there was insufficient evidence to support recommending one option over the other. This area was not prioritised as a research recommendation due to the small patient population.

Tricuspid regurgitation

A single, very small RCT was included in the review, which compared transcatheter repair + optimal medical therapy according to heart failure guidelines with optimal medical therapy alone in a population with severe, symptomatic tricuspid regurgitation and a high surgical risk score.

- Based on absolute effects, clinically important benefits of transcatheter repair were quality of life and NYHA class worsening by 1 or 2 classes at 3 months follow-up; however, there was uncertainty in the size of the effect for quality of life and the direction of effect for NYHA class worsening, meaning there was uncertainty as to whether the true difference was clinically important for quality of life and whether the true effect was actually a clinically important harm of transcatheter repair for NYHA class worsening. Clinically important harms were identified for in-hospital mortality and mortality at 12 months, haemorrhage at 30 days and reintervention at 48 h; however, uncertainty was present in the direction of effect for the mortality and haemorrhage outcomes and in the size of the effect for the reintervention outcome, meaning there was uncertainty as to whether the true effect was actually a clinically important benefit for the mortality and haemorrhage outcomes and whether the true difference was clinically important for reintervention. The results indicated no clinically

important difference between the two groups for the other outcomes reported in this study (rehospitalisation at 12 months and major vascular complications at 30 days), but there was uncertainty in this conclusion for both outcomes based on confidence intervals as upper and lower confidence intervals were consistent with a harm and benefit, respectively, of transcatheter repair for both outcomes.

Despite the relative and absolute effects suggesting possible clinically important benefits and harms of transcatheter repair in this population, this was a very small study, with only 14 participants randomised to each arm. This meant that imprecision and uncertainty in the direction or size of the effect was observed for all reported outcomes and the evidence was not sufficient to be able to inform recommendations. The committee discussed making recommendations for tricuspid regurgitation based on clinical practice and expertise but were not able to due to there being a lack of consensus in this area currently. A recommendation for research was instead made covering the management of tricuspid regurgitation with an indication for intervention (see Appendix J.1.5 for details).

1.7.2 Cost effectiveness and resource use

According to The Society for Cardiothoracic Surgery in Great Britain & Ireland there were a combined 10,000 isolated first-time aortic valve replacements in 2018/2019 with the number of TAVI cases roughly equal to half this number. A rough estimate provided by the committee is a ratio of 80:20 biological to mechanical valve ratio for aortic valve replacement, and 50:50 biological to surgical valves for mitral procedures.

Aortic stenosis:

Eight economic studies with relevant comparisons were included in this review. These were separated by operative risk. All were in a non-bicuspid population.

Inoperable (unsuitable for surgery):

Two cost-utility analyses included inoperable cohorts comparing transcatheter aortic valve implantation (TAVI) to medical management, with a UK NHS perspective. TAVI is a costly intervention especially the cost of the valve but there is a significant benefit in terms of survival. The two studies concluded that TAVI was cost effective in the base case. Both studies used the same RCT (PARTNER 1B) to inform the treatment effect. There were some differences between the studies in terms of their model structures, how utility data was incorporated and how observational data was used to inform some parameters that were not reported in the PARTNER 1B trial. Both studies were assessed as directly applicable with potentially serious limitation.

A third UK cost-utility analysis was excluded because the one-year survival and quality-adjusted life-years gained did not accurately reflect the evidence base.

The committee felt that the evidence was in favour of TAVI being cost effective for the inoperable population, and this was in line with current practice for this group of patients. Therefore, a recommendation was made to consider TAVI for inoperable patients.

Operable (suitable for surgery):

Seven of the studies included operable cohorts, (stratified by operative risk) comparing TAVI to surgical aortic valve replacement (SAVR). TAVI is a much more costly intervention due to the cost of the valve but there are fewer complications and faster recovery.

Two of these included studies had high operative risk groups. These two studies had conflicting results, with the cost per QALY gained £9,500 in one and £30,000 in the other.

Five studies included papers considered intermediate operative risk groups. Again, the conclusions across these studies were highly variable, ranging from TAVI dominating SAVR, to TAVI costing an extra £51,000 per QALY gained. A limitation common across all of these studies was that they used a single RCT to inform the treatment effect when seven eligible RCTs were includable from the clinical review. All four papers were assessed as partially applicable (none took a UK perspective) with potentially serious limitations.

Given the uncertainty in the results, and potential for a large resource impact, the committee agreed that original economic modelling was necessary for operable aortic stenosis (non-bicuspid), in order to make a recommendation.

The model found that TAVI was not cost effective compared to standard surgery in patients at high or intermediate operative risk for any age bands included. Low operative risk patients were not studied in the model but are expected to have similar outcomes and costs of patients at intermediate operative risk. The committee noted that the results of the model differed from some of the published studies. Four out of seven included cost-utility studies found TAVI compared to standard surgery to be cost-effective at £20,000 per QALY gained. The difference in the results was largely attributed to the

- the reintervention rate, which was substantially higher in the TAVI arm in the guideline model based on the results of the guideline's systematic review of trial evidence
- increased paravalvular leak (PVL) in the TAVI arm based on the results of the guideline's systematic review of trial evidence, which was associated with higher longer-term mortality in the guideline model
- the cost of the TAVI valve, which is higher in the UK than in some other countries.

Indeed, most of the published evidence assumed the same reintervention rate for TAVI and SAVR and no adverse effect on longer-term mortality due to PVL. Therefore, the published models seem to have under-estimated the incremental cost and over-estimated the QALYs associated with TAVI. However, even relaxing all 3 of those assumptions, the cost per QALY gain was persistently above £30,000. Following the discussion, the committee agreed to make a recommendation offering surgery as a first-line treatment for operable people with aortic stenosis with TAVI to be reserved for people for whom surgery is unsuitable.

Mixed/unclear aortic valve disease

One study that compared minimally invasive surgery (MIS) to standard surgery was included. The study was an RCT (MINI-STERN trial) study and was directly applicable to a UK NHS perspective. The study concluded that MIS was dominated by conventional surgery (MIS was more costly and gave less QALYs gain). A 12-month time horizon was used, however the committee agreed that there is unlikely to be a large difference in outcomes after 12 months. Despite this, limitations in the clinical evidence were highlighted, including small numbers of participants and small event numbers for many outcomes, and the results did not reflect the experience of the committee. As this health economic study was based on a single RCT, the same limitation therefore applies. The committee decided to recommend either conventional or minimally invasive surgery based on patient characteristics and preference and it was noted that lack of expertise in minimally invasive surgery locally should not be used as a reason for not performing a minimally invasive procedure and patients should be referred to a centre where there is expertise if this procedure is deemed most suitable for the patient.

Mitral regurgitation

A modelling analysis was undertaken to assess the cost-effectiveness of offering MitraClip to inoperable patients with severe mitral regurgitation secondary to heart failure. The analysis found MitraClip compared to medical management alone was not cost effective at a threshold of £20,000 per QALY and was slightly above £30,000 per QALY gained. The committee was presented with the results of the models together with the results of published analyses, which happened to have comparable results.

Three studies that compared percutaneous mitral valve repair (MitraClip) to medical management in a primary and secondary mitral regurgitation population were included.

The first study was assessed as directly applicable taking a UK NHS perspective, with potentially serious limitations and looking at a population with primary mitral regurgitation. The study found that MitraClip costs £22,153 per QALY gained compared to medical management. The committee agreed the study was of poor quality as it used registry data to inform the treatment effect. However, they thought that the cost per QALY gained was plausible, being lower than that found in the model looking at severe mitral regurgitation secondary to heart failure.

A second study on a mixed population with primary and secondary mitral regurgitation was assessed as partially applicable (Japanese public health care perspective) and with potentially serious limitations as relative treatment effects were informed from a propensity score matched study rather than a RCT. MitraClip was found to cost £13,549 per QALY gained, considerably lower than the UK study arguably due to differences in setting and population.

Finally, a third study on a population with secondary MR only was assessed as directly applicable taking a UK NHS perspective, with minor limitations. The relative treatment effects were based on the COAPT randomized controlled trial, the same source used for the NGC model and found MitraClip to cost £30,057 per QALY gained. The committee noted that the results were in line with the ones of the original modelling analysis, which was reassuring as both were based on the same RCT, looked at the same population and were conducted from an UK NHS perspective.

Following the discussion of the available evidence, the committee agreed to make a consider recommendation for transcatheter mitral repair for adults with primary mitral regurgitation. The cost per QALY gained was too high for MitraClip to be recommended for secondary mitral regurgitation at its current price.

Mixed/unclear mitral valve disease

One study that compared median sternotomy with minimally invasive surgery was included.

The study was assessed as partially applicable (Belgian perspective) with potentially serious limitations because it was a non-randomised retrospective analysis, the study found that minimally invasive surgery cost £411 less per person compared to full median sternotomy.

The committee agreed to recommend either median sternotomy or minimally invasive surgery based on patient characteristics and preference. It was noted that lack of expertise in minimally invasive surgery locally should not be used as a reason for not performing a minimally invasive procedure and patients should be referred to a centre where there is expertise if this procedure is deemed most suitable for the patient.

Mitral stenosis

No economic evidence was found for this subgroup. Transcatheter valvotomy for adults with rheumatic severe mitral stenosis is a long-established procedure, which is a less costly procedure than surgery and does not require patients to spend time in intensive care, Therefore, the committee made a recommendation in favour of transcatheter valvotomy for this population, which is in line with current practice.

1.7.3 Other factors the committee took into account

The committee highlighted the importance of discussing the risks and benefits of intervention in the context of shared decision making. As well as taking into consideration the needs and preferences of person, aspects specific to heart valve need to be discussed including the short and long-term benefits in terms of quality of life, valve durability, the risks associated

with the procedure, type of access and the possible need for other cardiac procedures in the future. A cross-reference to the NICE guideline on patient experience in adult NHS services was also made to enable shared decision making.

The committee noted that the vast majority of valve interventions would not be covered within RCTs as where there is an indication for intervention and patients are operable, it is well established that patients have poor outcomes if they are not operated on. For example, although no evidence was included in the review to compare transcatheter or surgical intervention with pharmacological or conservative management in operable aortic stenosis patients with a need for intervention, the committee considered that it is well established that interventions should be performed over conservative management and the reason there are no RCTs currently is because it would be unethical to include such a comparison within an RCT for the operable population. The committee highlighted that it is considered best practice for decisions on when to perform interventions and which intervention to perform to be made as part of a multidisciplinary heart team. However, it was also noted that in practice, the use of these and their structure vary. As the review did not investigate whether these decisions should be made by a multidisciplinary team and current practice varies, this detail was not incorporated into the recommendations.

The committee highlighted that people who misuse intravenous drugs are at a higher risk of developing endocarditis and requiring heart valve interventions. They highlighted the importance of support from services for the drug misuse and were aware of the NICE guideline on drug misuse: psychosocial interventions.

1.8 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1-1.5.13 and the research recommendations on interventions.

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Appendices

Appendix A: Review protocols

Table 40: Review protocol: transcatheter intervention, surgery or conservative management in heart valve disease

ID	Field	Content
0.	PROSPERO registration number	CRD42019147043
1.	Review title	What is the clinical and cost-effectiveness of transcatheter intervention, surgery (with mechanical or biological valves) and conservative management compared with each other for adults with heart valve disease?
2.	Review question	What is the clinical and cost-effectiveness of transcatheter intervention, surgery (with mechanical or biological valves) and conservative management compared with each other for adults with heart valve disease?
3.	Objective	To assess and compare the clinical and cost-effectiveness of transcatheter intervention, surgery (with mechanical or biological valves) and conservative management in adults with heart valve disease requiring intervention
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded

		• Validated study filters for systematic reviews and RCTs • No date restrictions applied The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Diagnosed heart valve disease in adults aged 18 years and over: Aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation.
6.	Population	Inclusion: Adults 18 years and over presenting with heart valve disease requiring intervention, stratified by disease type as follows: • aortic stenosis (non-bicuspid) • aortic stenosis (bicuspid) • aortic stenosis (mixed non-bicuspid and bicuspid or unclear) • aortic regurgitation (non-bicuspid) • aortic regurgitation (bicuspid) • aortic regurgitation (mixed non-bicuspid and bicuspid or unclear) • mitral stenosis • mitral regurgitation • tricuspid regurgitation A threshold of 75% will be used to assign studies to the above strata. For example, to be assigned to the tricuspid regurgitation stratum, 75% of the population of a study would have to have tricuspid regurgitation as the type of heart valve disease driving the need for intervention.

		For populations with multiple valve disease, studies will be classified into strata based on the heart valve disease that drives the need for intervention (e.g. most severe valve disease). Only those undergoing their first intervention for heart valve disease (either surgical or transcatheter) will be included – studies where ≥10% of one or more of the groups have had previous attempts at surgical or transcatheter management prior to the trial will not be included. However, trials where patients have previously received medical management will not be excluded from this review. For studies where at least one of the arms is a replacement intervention, they will not be excluded if ≥10% had received a previous repair procedure but will be downgraded for indirectness. Exclusion: • Children (aged <18 years). • Adults with congenital heart disease (excluding bicuspid aortic valves). • Tricuspid stenosis and pulmonary valve disease. • Patients undergoing a second or greater number of surgical or transcatheter interventions for heart valve disease
7.	Intervention/Exposure/Test	• Transcatheter repair • Transcatheter replacement with biological valves • Minimally invasive surgery repair • Minimally invasive surgery replacement with biological or mechanical valves • Standard surgery repair • Standard surgery replacement with biological or mechanical valves Note: Transcatheter intervention and surgical interventions will be stratified by repair and replacement. Within the replacement interventions, biological and mechanical valves will be pooled.

		Note: Sutureless valves will be included within both the standard and minimally invasive surgery interventions as reported in the studies Primary studies with a mixed intervention (some in the 'active' arm received the intervention of interest and some a different intervention) will be included if at least 90% received the intervention of interest.
8.	Comparator/Reference standard/Confounding factors	Conservative management (for example, medical management/treatment or no treatment) Other active comparator listed above
9.	Types of study to be included	Randomised controlled trials (RCTs) or systematic reviews of RCTs If no RCT data are available, observational data will not be considered for this review. This is due to the risk of confounding variables influencing the study results, reducing our confidence in the review results
10.	Other exclusion criteria	Exclusion criteria: • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study. • Non randomised studies / observational studies • Non-English language studies
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• All-cause mortality at ≥12 months • Cardiac mortality at ≥12 months • Intervention-related mortality at 30 days • Health-related quality of life at ≥12 months • Onset or exacerbation of heart failure at ≥12 months • Intervention-related stroke or TIA at 30 days • Intervention-related major bleeding at 30 days • Need for re-intervention at ≥12 months

		Follow-up: • Pool outcomes reported at the time-points specified above and take the latest reported time-point for the ≥12 months' time-point if multiple time points reported in a single study
13.	Secondary outcomes (important outcomes)	• Length of stay (following initial intervention) • Re-hospitalisation at ≥12 months • Intervention-related pacemaker implantation at 30 days • Intervention-related atrial fibrillation at 30 days • Intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication) • Prosthetic valve endocarditis at ≥12 months Follow-up: • Pool outcomes reported at the time-points specified above and take the latest reported time-point for the ≥12 months' time-point if multiple time points reported in a single study
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study

		quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. MS Excel will be used for data extraction and critical appraisal for health economic studies.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Checklists used in this intervention review are as follows for different types of study design: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third party where necessary.
16.	Strategy for data synthesis	• Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome.

		• Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. A second reviewer will quality assure 10% of the data analyses. Discrepancies will be identified and resolved through discussion (with a third party where necessary).
17.	Analysis of sub-groups	**Groups that will be analysed separately (strata):** <u>Population – disease type</u> Adults 18 years and over presenting with heart valve disease requiring intervention, stratified by disease type as follows: • aortic stenosis (non-bicuspid) • aortic stenosis (bicuspid) • aortic regurgitation (non-bicuspid) • aortic regurgitation (bicuspid) • mitral stenosis • mitral regurgitation • tricuspid regurgitation

		Intervention Transcatheter intervention and surgical interventions will be stratified by repair and replacement. Within the replacement interventions, biological and mechanical valves will be pooled. Additionally, surgical interventions will be stratified by the invasiveness of the procedure, generating the following strata based on intervention: • Transcatheter repair • Transcatheter replacement with biological valves • Minimally invasive surgery repair • Minimally invasive surgery replacement with biological or mechanical valves • Standard surgery repair • Standard surgery replacement with biological or mechanical valves **Subgroups that will be investigated if heterogeneity is present:** • Age (<75 vs. ≥75 years) • Women of childbearing age vs. those not of childbearing age (<45 vs. ≥45 years) • For aortic stenosis and mitral regurgitation: operative risk (low, intermediate, high, inoperable) • For aortic regurgitation: presence vs. absence of severe systolic dysfunction (LVEF ≤35% vs. >35%) • For mitral stenosis: morphology suitable for transcatheter intervention vs. morphology not suitable for transcatheter intervention • For mitral regurgitation and tricuspid regurgitation: primary vs. secondary valve disease • For surgical (minimally invasive or standard) replacement, mechanical vs. biological valves

<table>
<tr><td></td><td></td><td colspan="3">• For aortic stenosis: Different routes of transcatheter intervention (transfemoral, transapical and sub-clavian)

Studies will be assigned to different subgroups using a threshold of 75% - for example, a study in which 80% of the population have primary valve disease and 20% have secondary valve disease would be assigned to the primary valve disease group when subgrouping for this factor.</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td></td><td></td><td colspan="2"></td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">09/05/2019</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">17/06/2021</td></tr>
<tr><td rowspan="4">23.</td><td rowspan="4">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
</table>

		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail HVD@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain [Guideline lead] Eleanor Samarasekera [Senior systematic reviewer] Nicole Downes [Systematic reviewer] George Wood [Systematic reviewer] Robert King [Health economist] Jill Cobb [Information specialist] Katie Broomfield [Project manager]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must		

		declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122	
29.	Other registration details	None	
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Aortic regurgitation; Aortic stenosis; Biological heart valve; Heart valve disease; Heart valve repair; Heart valve replacement; Intervention; Mechanical heart valve; Mitral regurgitation; Mitral stenosis; Surgical valve replacement; Transcatheter valve replacement; Tricuspid regurgitation	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing

		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

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2 **Table 41: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[267] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable).

	• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

Heart valve disease – search strategy 8 - transcatheter intervention, surgery or conservative management

This literature search strategy was used for the following review:

- What is the clinical and cost-effectiveness of transcatheter intervention, surgery (with mechanical or biological valves) and conservative management compared with each other for adults with heart valve disease?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[267]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 42: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 10 of 12 CENTRAL to 2020 Issue 10 of 12	None

Medline (Ovid) search terms

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/

23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	random*.ti,ab.
35.	factorial*.ti,ab.
36.	(crossover* or cross over*).ti,ab.
37.	((doubl* or singl*) adj blind*).ti,ab.
38.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
39.	crossover procedure/
40.	single blind procedure/
41.	randomized controlled trial/
42.	double blind procedure/
43.	or/34-42
44.	systematic review/
45.	meta-analysis/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/44-53
56.	33 and (43 or 55)
57.	exp heart surgery/
58.	exp valvular heart disease/su [Surgery]
59.	exp heart valve prosthesis/ or exp heart valve replacement/
60.	exp catheterization/
61.	exp minimally invasive surgery/
62.	((transcatheter or surg* or intervention*) adj3 (repair* or replac* or implant*)).ti,ab.
63.	(TAVR or TAVI or TMVR or TMVI).ti,ab.
64.	((cardiovascular or cardiac or heart or robotic) adj2 surg*).ti,ab.

65.	(commissurotomy or valvulotomy or valvotomy or valvuloplasty or valvoplasty or annuloplasty).ti,ab.
66.	(sternotomy or ministernotomy or mini-sternotomy or thoracotomy or port access or non-sternotomy).ti,ab.
67.	(mitra clip or MitraClip or edge to edge or chord* or balloon).ti,ab.
68.	or/57-67
69.	56 and 68

1 **Embase (Ovid) search terms**

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	random*.ti,ab.

35.	factorial*.ti,ab.
36.	(crossover* or cross over*).ti,ab.
37.	((doubl* or singl*) adj blind*).ti,ab.
38.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
39.	crossover procedure/
40.	single blind procedure/
41.	randomized controlled trial/
42.	double blind procedure/
43.	or/34-42
44.	systematic review/
45.	meta-analysis/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/44-53
56.	33 and (43 or 55)
57.	exp heart surgery/
58.	exp valvular heart disease/su [Surgery]
59.	exp heart valve prosthesis/ or exp heart valve replacement/
60.	exp catheterization/
61.	exp minimally invasive surgery/
62.	((transcatheter or surg* or intervention*) adj3 (repair* or replac* or implant*)).ti,ab.
63.	(TAVR or TAVI or TMVR or TMVI).ti,ab.
64.	((cardiovascular or cardiac or heart or robotic) adj2 surg*).ti,ab.
65.	(commissurotomy or valvulotomy or valvotomy or valvuloplasty or valvoplasty or annuloplasty).ti,ab.
66.	(sternotomy or ministernotomy or mini-sternotomy or thoracotomy or port access or non-sternotomy).ti,ab.
67.	(mitra clip or MitraClip or edge to edge or chord* or balloon).ti,ab.
68.	or/57-67
69.	56 and 68

1 **Cochrane Library (Wiley) search terms**

#2.	MeSH descriptor: [Heart Valve Diseases] explode all trees
#3.	MeSH descriptor: [Heart Valves] explode all trees
#4.	((primary or secondary) NEXT valv* disease*):ti,ab
#5.	((valv* or flap* or leaflet*) near/1 (heart or cardiac) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab

#6.	((mitral or aortic or tricuspid or pulmon*) NEXT (valv* or flap* or leaflet*) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#7.	((mitral or aortic or tricuspid or pulmon*) NEAR/3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)):ti,ab
#8.	MeSH descriptor: [Heart Valve Prosthesis] explode all trees
#9.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) NEXT (valv* or flap* or leaflet*)):ti,ab
#10.	valve-in-valve:ti,ab
#11.	(transcatheter NEAR/2 (valve or valves)):ti,ab
#12.	MeSH descriptor: [Heart Murmurs] explode all trees
#13.	((heart or cardiac) NEXT murmur*):ti,ab
#14.	(or #1-#12)
#15.	MeSH descriptor: [Cardiac Surgical Procedures] explode all trees
#16.	MeSH descriptor: [Heart Valve Diseases] explode all trees and with qualifier(s): [surgery - SU]
#17.	MeSH descriptor: [Heart Valve Prosthesis Implantation] explode all trees
#18.	MeSH descriptor: [Catheterization] explode all trees
#19.	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees
#20.	((transcatheter or surg* or intervention*) near/3 (repair* or replac* or implant*)):ti,ab
#21.	(TAVR or TAVI or TMVR or TMVI):ti,ab
#22.	((cardiovascular or cardiac or heart or robotic) near/2 surg*):ti,ab
#23.	(commissurotomy or valvulotomy or valvotomy or valvuloplasty or valvoplasty or annuloplasty):ti,ab
#24.	(sternotomy or ministernotomy or mini-sternotomy or thoracotomy or port access or non-sternotomy):ti,ab
#25.	(mitra NEXT clip or MitraClip or "edge to edge" or chord* or balloon):ti,ab
#26.	(or #14-#24)
#27.	#13 and #25

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to heart valve disease population in NHS Economic Evaluation Database (NHS EED) – (this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) – (this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 43: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Embase	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

1 Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/
18.	Anecdotes as Topic/
19.	comment/
20.	case report/
21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to English language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	Economics/
37.	Value of life/

38.	exp "Costs and Cost Analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, Medical/
41.	Economics, Nursing/
42.	Economics, Pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp Budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51
53.	35 and 52

1 **Embase (Ovid) search terms**

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/

24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47

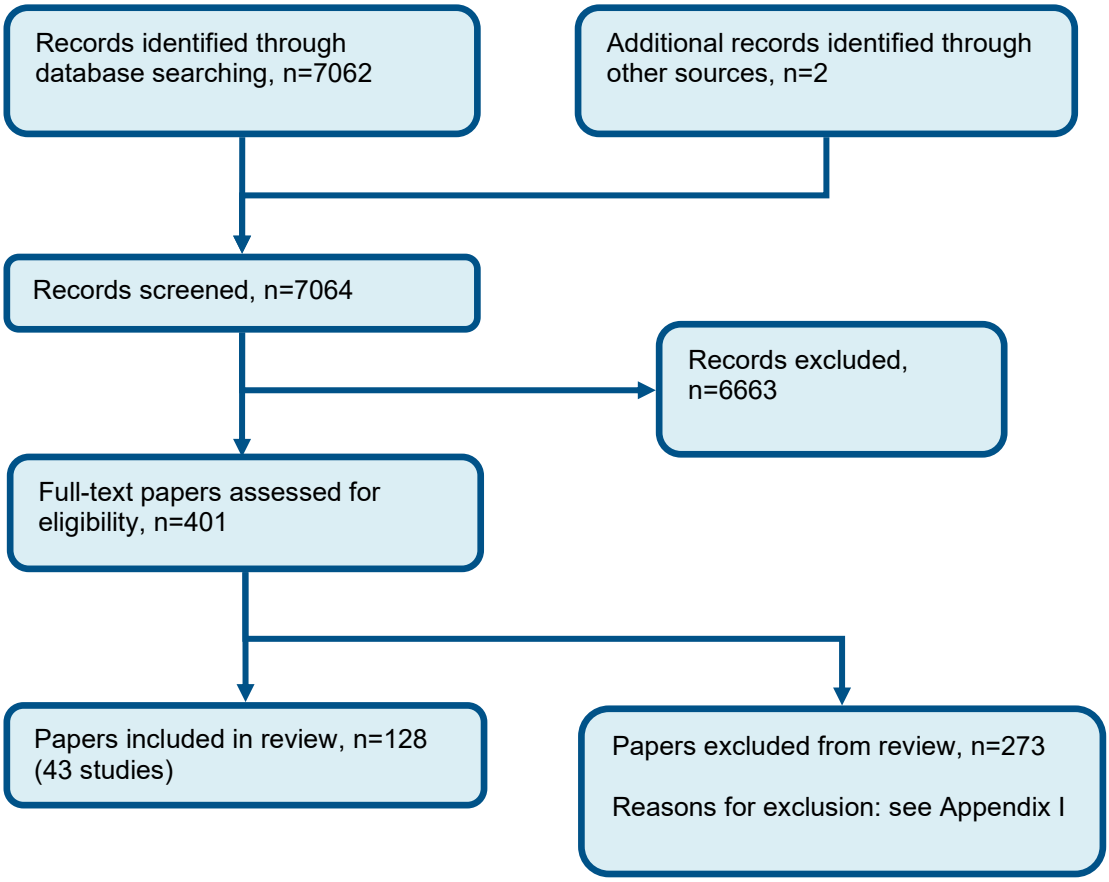
1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Heart Valves EXPLODE ALL TREES
#3.	(((primary or secondary) adj Valv* adj disease*))
#4.	(((valv* or flap* or leaflet*) adj (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#5.	((heart or cardiac) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*))
#6.	(((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#7.	(((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)))
#8.	MeSH DESCRIPTOR Heart Valve Prosthesis EXPLODE ALL TREES
#9.	(((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)))
#10.	(valve-in-valve)
#11.	((transcatheter adj2 (valve or valves)))
#12.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

2

Appendix C: Clinical evidence selection

Figure 3: Flow chart of clinical study selection for the review of the clinical and cost-effectiveness of transcatheter intervention, surgery (with mechanical or biological valves) and conservative management compared with each other for adults with heart valve disease



Appendix D: Clinical evidence tables

Study (subsidiary papers)	Acker 2014[1] (Goldstein 2016[140], Perrault 2012[289])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=251)
Countries and setting	Conducted in Canada, USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Up to 2 years follow-up available
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Resting transthoracic echocardiography
Stratum	Mitral regurgitation: Adults with severe ischaemic mitral regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic, severe ischaemic mitral regurgitation and coronary artery disease eligible for surgical repair or replacement of mitral valve with or without coronary artery bypass grafting;
Exclusion criteria	Any echocardiographic evidence of structural (chordal or leaflet) mitral valve disease or ruptured papillary muscle.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Repair, 69 (10) years; replacement, 68 (9) years. Gender (M:F): Repair, 77/49; replacement, 78/47. Ethnicity: White: repair, 82.5%; replacement, 78.4%; Hispanic: repair, 10.3%; replacement, 8.8%

Further population details	1. Age: <75 years (Mean age in both groups <75 years). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear (Operative risk not mentioned.). 5. Primary vs secondary valve disease (for MR and TR): Secondary (Functional/ischaemic disease rather than structural.). 6. Systolic dysfunction (for AR): Not applicable
Extra comments	Medical and surgical history: diabetes (38.1 vs. 32.8%), renal insufficiency (23.0 vs. 32.0%), previous CABG (19.0 vs. 18.4%), previous PCI (39.7 vs. 32.0%), heart failure (69.8 vs. 73.6%), atrial fibrillation (35.7 vs. 28.0%), implantable cardioverter-defibrillator (18.3 vs. 13.6%), stroke (11.1 vs. 8.8%); mean (SD) LVEF, 42.4 (12.0) vs. 40.0 (11.0)%; mean (SD) effective regurgitant orifice area, 0.40 (0.17) vs. 0.39 (0.11) cm^2; CCS angina scale: no angina (45.2 vs. 56.0%) and grade III/IV (24.6 vs. 16.8%); NYHA class III/IV, 57.6 vs. 61.3%; mean (SD) Minnesota Living with Heart Failure score, 46.1 (27.2) vs. 50.0 (27.4); concomitant procedure: CABG (73.8 vs. 75.2%), tricuspid valve repair (12.7 vs. 17.6%) and atrial maze (11.9 vs. 12.8%)
Indirectness of population	No indirectness
Interventions	(n=126) Intervention 1: Surgical repair (unclear/mixed invasiveness). Surgical mitral valve repair with or without coronary artery bypass grafting. All valve procedures performed with full or partial sternotomy or with a right thoracotomy with cardiopulmonary bypass according to local standards. Exposure of the mitral valve accomplished by either the left atrial (Waterston groove) or biatrial approach. Mitral valve repair accomplished using an approved rigid or semirigid undersized complete annuloplasty ring. The ring size is determined by the surface area of the anterior mitral leaflet as measured by the intertrigonal distance and anterior leaflet height. The type of ring used was based on the preference of the operating surgeon. A subvalvular procedure could be performed if tethering was present. Duration N/A - surgical procedure. Concurrent medication/care: If required, coronary artery bypass grafting performed using standard techniques and 2-stage venous cannulation. All patients were to receive guideline-directed medical therapy by their treating cardiologist, including aspirin, lipid-lowering agents, beta-blockers, and angiotensin-converting–enzyme inhibitors, as well as cardiac-resynchronization therapy. Indirectness: Serious indirectness; Indirectness comment: Mixture of minimally invasive and standard surgery - unclear Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter procedure). 2. Valve type: Not applicable (Repair rather than replacement procedure). (n=125) Intervention 2: Surgical replacement with biological or mechanical valve (unclear/mixed

	invasiveness). Surgical mitral valve replacement with or without coronary artery bypass grafting. All valve procedures performed with full or partial sternotomy or with a right thoracotomy with cardiopulmonary bypass according to local standards. Exposure of the mitral valve accomplished by either the left atrial (Waterston groove) or biatrial approach. Mitral valve replacement included complete preservation of the subvalvular apparatus. The technique of preservation, type of prosthetic valve, and technique of suture placement were chosen according to the preference of the surgeon. Duration N/A - surgical procedure. Concurrent medication/care: If required, coronary artery bypass grafting performed using standard techniques and 2-stage venous cannulation. All patients were to receive guideline-directed medical therapy by their treating cardiologist, including aspirin, lipid-lowering agents, beta-blockers, and angiotensin-converting–enzyme inhibitors, as well as cardiac-resynchronization therapy. Indirectness: Serious indirectness; Indirectness comment: Mixture of minimally invasive and standard surgery - unclear Further details: 1. Route of transcatheter intervention (in TAVI for AS): 2. Valve type:
Funding	Academic or government funding (Supported by a cooperative agreement (U01 HL088942) with the National Heart, Lung, and Blood Institute and the National Institute of Neurological Diseases and Stroke, National Institutes of Health, and by the Canadian Institutes of Health Research.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SURGICAL REPAIR (UNCLEAR/MIXED INVASIVENESS) versus SURGICAL REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE (UNCLEAR/MIXED INVASIVENESS)

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral regurgitation: Deaths, all-cause at 2 years; Group 1: 24/114, Group 2: 29/113
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12; Group 2 Number missing: 12
- Actual outcome for Mitral regurgitation: Deaths, all-cause at 2 years; Group 1: Observed events 24 n=126 ; Group 2: Observed events 29 n=125; HR 0.79; Lower CI 0.46 to Upper CI 1.35; Test statistic: P=0.39
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Incomplete outcome: time-to-event data with censoring for those missing.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12; Group 2 Number missing: 12

Protocol outcome 2: Intervention-related mortality at 30 days

- Actual outcome for Mitral regurgitation: Deaths, all-cause at 30 days; Group 1: 2/126, Group 2: 5/125
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Potentially missing data but unclear at this time-point. ; Group 2 Number missing: , Reason: Potentially missing data but unclear at this time-point.

Protocol outcome 3: Quality of life at ≥12 months
- Actual outcome for Mitral regurgitation: Minnesota Living with Heart Failure questionnaire at 1 year; Group 1: mean 24.5 (SD 23.1); n=95, Group 2: mean 19.6 (SD 19.4); n=85; Minnesota Living with Heart Failure questionnaire 0-105 Top=High is poor outcome; Comments: Baseline values: surgical repair, 46.1 (27.2, n=126); surgical replacement, 50.0 (27.4, n=126)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Score is comparable at baseline between the two groups, though slightly higher in the replacement group; Group 1 Number missing: 31, Reason: withdrawal before 12 months (n=3); death before 12 months (n=18); remaining may not have completed questionnaire (n=10); Group 2 Number missing: 40, Reason: withdrawal before 12 months (n=1); death before 12 months (n=22); remaining may not have completed questionnaire (n=17)
- Actual outcome for Mitral regurgitation: SF-12 physical component at 1 year; Group 1: mean 43.6 (SD 8.1); n=93, Group 2: mean 44.2 (SD 7.1); n=85; Study 12-Item Short Form Health Survey (SF-12) - physical function 0-100 Top=High is good outcome; Comments: Baseline values: surgical repair, 37.3 (8.1, n=126); surgical replacement, 37.2 (7.2, n=125)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Score is comparable at baseline between the two groups.; Group 1 Number missing: 33, Reason: withdrawal before 12 months (n=3); death before 12 months (n=18); remaining may not have completed questionnaire (n=12); Group 2 Number missing: 40, Reason: withdrawal before 12 months (n=1); death before 12 months (n=22); remaining may not have completed questionnaire (n=17)
- Actual outcome for Mitral regurgitation: SF-12 mental component at 1 year; Group 1: mean 46.8 (SD 7.1); n=93, Group 2: mean 46.9 (SD 6.4); n=85; Study 12-Item Short Form Health Survey (SF-12) - mental function 0-100 Top=High is good outcome; Comments: Baseline values: surgical repair, 47.9 (7.7, n=126); surgical replacement, 47.8 (9.1, n=125)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Score is comparable at baseline between the two groups.; Group 1 Number missing: 33, Reason: withdrawal before 12 months (n=3); death before 12 months (n=18); remaining may not have completed questionnaire (n=12); Group 2 Number missing: 40, Reason: withdrawal before 12 months (n=1); death before 12 months (n=22); remaining may not have completed questionnaire (n=17)
- Actual outcome for Mitral regurgitation: EQ-5D at 1 year; Group 1: mean 73.7 (SD 16.3); n=91, Group 2: mean 73.9 (SD 20.1); n=80; EuroQol Group 5-Dimension Self-Report Questionnaire 0-100 Top=High is good outcome; Comments: Baseline values: surgical repair, 53.0 (24.6, n=126); surgical

replacement, 53.8 (23.3, n=125)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Score is comparable at baseline between the two groups.; Group 1 Number missing: 35, Reason: withdrawal before 12 months (n=3); death before 12 months (n=18); remaining may not have completed questionnaire (n=14); Group 2 Number missing: 45, Reason: withdrawal before 12 months (n=1); death before 12 months (n=22); remaining may not have completed questionnaire (n=22)

Protocol outcome 4: Onset or exacerbation of heart failure at ≥12 months
- Actual outcome for Mitral regurgitation: Worsening NYHA class (increase of ≥1 grade) at 2 years; Group 1: 5/85, Group 2: 5/84
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Missing data but rate unclear; Group 2 Number missing: , Reason: Missing data but rate unclear

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral regurgitation: Stroke at 30 days; Group 1: 3/126, Group 2: 4/125
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Potentially missing data but unclear at this time-point. ; Group 2 Number missing: , Reason: Potentially missing data but unclear at this time-point.

Protocol outcome 6: Need for re-intervention at ≥12 months
- Actual outcome for Mitral regurgitation: Mitral valve reintervention at 2 years; Group 1: 10/126, Group 2: 1/125; Comments: Includes those that failed index mitral valve procedure (because the repair procedure did not sufficiently correct MR and were subsequently converted to valve replacement) and those that had mitral valve reoperation
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Missing data but rate unclear; Group 2 Number missing: , Reason: Missing data but rate unclear

Protocol outcome 7: Length of hospital stay at after intervention
- Actual outcome for Mitral regurgitation: Length of stay following surgery at Postoperative; Group 1: mean 11.5 (SD 9); n=126, Group 2: mean 11.9 (SD 8.6); n=125
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 8: Prosthetic valve endocarditis at ≥12 months - Actual outcome for Mitral regurgitation: Endocarditis at 2 years; Group 1: 0/126, Group 2: 2/125 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: , Reason: Missing data but rate unclear; Group 2 Number missing: , Reason: Missing data but rate unclear Protocol outcome 9: Renal failure at 30 days - Actual outcome for Mitral regurgitation: Renal failure, rate ratio at 30 days; Group 1: 3/126, Group 2: 9/125; Comments: Note that event rate includes some who may have had the event more than once. Study also gives number of events per 100 patient-years, which will use for analysis: surgical repair, 28.8; surgical replacement, 87.8. Rate ratio: 0.32801822 Person-years in each group: surgical repair, 10.416667; surgical replacement, 10.2505695. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Outcome reporting: only total events reported for each group rather than number of people with the event.; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Potentially missing data but unclear at this time-point. ; Group 2 Number missing: , Reason: Potentially missing data but unclear at this time-point.	
Protocol outcomes not reported by the study	Cardiac mortality at ≥12 months; Intervention-related major bleeding at 30 days; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Major vascular complications at 30 days

Study (subsidiary papers)	**Adams 2014[2], Gleason 2018[135], Arnold 2015[25], Conte 2017[85], Deeb 2016[95], Gaudiani 2017[130], Gleason 2016[136], Grayburn 2018[144], Kadkhodayan 2017[177], Little 2016[221], Reardon 2015[308], Reardon 2016[310], Reynolds 2016[315], Zorn 2016[439], Arnold 2020[22])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=795)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Specific echocardiographic parameters fitting with our protocol
Stratum	Aortic stenosis (non-bicuspid):
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects with co-morbidities such that one cardiologist and two cardiac surgeons agree predicted risk of operative mortality is ≥15% at 30 days. Senile degenerative aortic stenosis with a mean gradient >40mmHg or jet velocity greater than 4.0m/s, and an initial aortic valve area of less than or equal to 0.8cm² or aortic valve area index less than or equal to 0.5cm²/m², NYHA class II or greater, can give informed consent.
Exclusion criteria	Evidence of acute MI less than or equal to 30 days before intervention, any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to intervention with bare metal stents and 6 months for drug eluting stents, blood dyscrasias, untreated clinically significant coronary artery disease requiring revascularisation, cardiogenic shock, need for emergency surgery for any reason, severe ventricular dysfunction with LVEF <20%, recent CVA or TIA, end stage renal disease, GI bleeding within the past 3 months, a known hypersensitivity or contraindication to aspirin, heparin, nitinol, ticlopidine and clopidogrel, and

	contrast media, ongoing sepsis (including active endocarditis), subject refuses a blood transfusion, life expectance <12 months due to associated non-cardiac comorbid conditions, other medical, social or psychological conditions that in the opinion of an investigator precludes the subject from appropriate consent, severe dementia, currently participating in an investigational drug or another device trial, symptomatic carotid or vertebral artery disease, subject has been offered surgical aortic valve replacement but declines, native aortic annulus size <18mm or >29mm, pre-existing prosthetic heart valve in any position, mixed aortic valve disease, moderate to severe mitral regurgitation or tricuspid regurgitation, moderate to severe mitral stenosis, hypertrophic obstructive cardiomyopathy, echocardiographic evidence of intracardiac mass, thrombus or vegetation, severe basal septal hypertrophy with an outflow gradient, aortic root angulation (>70degree angle for femoral and left subclavian access or >30 degrees for right subclavian/axillary access), ascending aorta exceeding the maximum diameter for any given native aortic annulus, congenital bicuspid or unicuspid valve, sinus of Valsalva anatomy that would prevent adequate coronary perfusion, transarterial access not able to accomodate an 18F sheath
Recruitment/selection of patients	The first three patients were enrolled as "roll-in" participants with subsequent patients being randomised.
Age, gender and ethnicity	Age - Mean (SD): Intervention: 83.2±7.1, control: 83.5±6.3. Gender (M:F): 423:372. Ethnicity: Not stated
Further population details	1. Age: 75 years or over (Based on mean age and confidence intervals being above 75 years). 2. Childbearing age: Women not of childbearing age (≥45 years) 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): High (STS PROM estimate TAVR group: 7.3±3.0, SAVR group: 7.5±3.2. Logistic EuroSCORE TAVR group: 17.6±13.0, SAVR group: 18.4±12.8). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=394) Intervention 1: Transcatheter replacement with biological valves. With the CoreValve device. Duration N/A - Surgical procedure. Concurrent medication/care: After the procedure, started on aspirin 81mg daily and clopidogrel 75mg daily for 3 months, followed by monotherapy at the same dose indefinitely. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not stated / Unclear (Includes both iliofemoral and noniliofemoral. Patients were randomised after stratification into surgery type required.). 2. Valve type: Biological

	(n=401) Intervention 2: Standard surgery replacement with biological or mechanical valves. Conventional surgical technique. Choice of type and size of valve was left to the operating surgeon. Duration N/A - surgical procedure. Concurrent medication/care: Patients were started on aspirin at least 81mg daily after surgery to be continued indefinitely (including those requiring warfarin). Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (No statement as to the type of valve used. Left to surgeon discretion.).
Funding	Study funded by industry (Medtronic)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPLACEMENT WITH BIOLOGICAL VALVES versus STANDARD SURGERY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): All-cause mortality at 5 years; Group 1: Observed events 208 n=391 ; Group 2: Observed events 184 n=359; HR 0.93; Lower CI 0.77 to Upper CI 1.14; Log rank variance: 0.50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: 394 patients assigned to TAVR. 391 underwent TAVR. 2 exited during the first year of follow up. 3 exited during the second year of follow up with 1 pending follow up. 8 exited during the third year of follow up with 3 pending follow up. 18 additional patients not available for follow up during the third year.; Group 2 Number missing: 73, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR. 9 exited the trial in the first year. 13 exited during the second year. 1 pending follow-up in the second year. 8 exited during the second year. 15 additional patients not available for follow up during the third year.
- Actual outcome for Aortic stenosis (non-bicuspid): All-cause mortality at 5 years; Group 1: 208/391, Group 2: 184/359
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: 394 patients assigned to TAVR. 391 underwent TAVR. 2 exited during the first year of follow up. 3 exited during the second year of follow up with 1 pending follow up. 8 exited during the third year of follow up with 3 pending follow up. 18 additional patients not available for follow up during the third year.; Group 2 Number missing: 73, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR. 9 exited the trial in the first year. 13 exited during the second year. 1 pending follow-up in the second year. 8 exited during the second year. 15 additional patients not available for follow up during the third year.

Protocol outcome 2: Cardiac mortality at ≥12 months

- Actual outcome for Aortic stenosis (non-bicuspid): Cardiac mortality at 5 years; Group 1: Observed events 134 n=391 ; Group 2: Observed events 115 n=359; HR 0.97; Lower CI 0.75 to Upper CI 1.24; Log rank variance: 0.80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: 394 patients assigned to TAVR. 391 underwent TAVR. 2 exited during the first year of follow up. 3 exited during the second year of follow up with 1 pending follow up. 8 exited during the third year of follow up with 3 pending follow up. 18 additional patients not available for follow up during the third year.; Group 2 Number missing: 73, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR. 9 exited the trial in the first year. 13 exited during the second year. 1 pending follow-up in the second year. 8 exited during the second year. 15 additional patients not available for follow up during the third year.
- Actual outcome for Aortic stenosis (non-bicuspid): Cardiac mortality at 5 years; Group 1: 134/391, Group 2: 115/359
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: 394 patients assigned to TAVR. 391 underwent TAVR. 2 exited during the first year of follow up. 3 exited during the second year of follow up with 1 pending follow up. 8 exited during the third year of follow up with 3 pending follow up. 18 additional patients not available for follow up during the third year.; Group 2 Number missing: 73, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR. 9 exited the trial in the first year. 13 exited during the second year. 1 pending follow-up in the second year. 8 exited during the second year. 15 additional patients not available for follow up during the third year.

Protocol outcome 3: Interevention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): All-cause mortality at 30 days; Group 1: 13/390, Group 2: 16/357
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 394 patients assigned to TAVR. 390 underwent TAVR (reported in Adams paper, 1 additional patient becomes apparent in follow up papers but data is not available for this patient).; Group 2 Number missing: 44, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR (reported in Adams paper, 6 additional patients become apparent in follow up papers but data is not available for this patient).

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): KCCQ overall at 5 years; Group 1: mean 66.5 (SD 21.3); n=100, Group 2: mean 66 (SD 20.4); n=88; KCCQ overall 0-100 Top=High is good outcome; Comments: Baseline values: TAVR, 46.8 (23.4, n=376); AVR, 46.4 (22.2, n=331). Reported in supplementary tables of Gleason 2018 paper.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 294; Group 2 Number missing: 313
- Actual outcome for Aortic stenosis (non-bicuspid): SF-12 physical at 5 years; Group 1: mean 32.8 (SD 10.8); n=92, Group 2: mean 33.2 (SD 8.7); n=81; SF-12 physical 0-100 Top=High is good outcome; Comments: Reported in supplementary tables of Gleason 2018 paper. Baseline values: TAVR, 30.7 (9.2, n=362); AVR, 30.9 (8.5, n=313)

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 302; Group 2 Number missing: 320
- Actual outcome for Aortic stenosis (non-bicuspid): SF-12 mental at 5 years; Group 1: mean 50.4 (SD 10.8); n=92, Group 2: mean 50.5 (SD 11.2); n=81; SF-12 mental 0-100 Top=High is good outcome; Comments: As reported in supplementary tables of Gleason 2018 paper. Baseline values: TAVR, 47.4 (12, n=362); AVR, 48.3 (11.6, n=313)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 302; Group 2 Number missing: 320
- Actual outcome for Aortic stenosis (non-bicuspid): EQ-5D at 1 year; Group 1: mean 0.784 (SD 0.183); n=248, Group 2: mean 0.78 (SD 0.182); n=193; EQ-5D utility 0-1 Top=High is good outcome; Comments: As reported in supplementary table of Arnold paper. Baseline values: TAVR, 0.732 (0.196, n=371); AVR, 0.732 (0.181, n=332)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 146; Group 2 Number missing: 208

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Stroke at 30 days; Group 1: 19/390, Group 2: 22/357
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 394 patients assigned to TAVR. 390 underwent TAVR (reported in Adams paper, 1 additional patient becomes apparent in follow up papers but data is not available for this patient).; Group 2 Number missing: 44, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR (reported in Adams paper, 6 additional patients become apparent in follow up papers but data is not available for this patient).

Protocol outcome 6: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major bleeding at 30 days; Group 1: 109/390, Group 2: 123/357
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 394 patients assigned to TAVR. 390 underwent TAVR (reported in Adams paper, 1 additional patient becomes apparent in follow up papers but data is not available for this patient).; Group 2 Number missing: 44, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR (reported in Adams paper, 6 additional patients become apparent in follow up papers but data is not available for this patient).

Protocol outcome 7: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Reintervention at 5 years; Group 1: 10/391, Group 2: 2/359; Comments: As-treated results from Gleason 2018 paper.
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34, Reason: 394 patients assigned to TAVR. 391 underwent TAVR. 31 patients in the TAVR group said to have left the trial but were still included in the as-treated analysis.; Group 2 Number missing: 128, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR. 86 patients in the SAVR group said to have left the trial but were still included in the as-treated analysis.

Protocol outcome 8: Re-hospitalisation at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Aortic valve hospitalisation at 5 years; Group 1: 120/391, Group 2: 83/359; Comments: As-treated results from Gleason 2018 paper.
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34, Reason: 394 patients assigned to TAVR. 391 underwent TAVR. 31 patients in the TAVR group said to have left the study but were included in the as-treated analysis.; Group 2 Number missing: 128, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR. 86 patients in the SAVR group said to have left the study but were included in the as-treated analysis.

Protocol outcome 9: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Permanent pacemaker implantation at 30 days; Group 1: 76/390, Group 2: 25/357
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 394 patients assigned to TAVR. 390 underwent TAVR (reported in Adams paper, 1 additional patient becomes apparent in follow up papers but data is not available for this patient).; Group 2 Number missing: 44, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR (reported in Adams paper, 6 additional patients become apparent in follow up papers but data is not available for this patient).

Protocol outcome 10: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New-onset or worsening atrial fibrillation at 30 days; Group 1: 45/390, Group 2: 108/357
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Adds in patients with worsening atrial fibrillation unlike other evidence which does not report this group; Group 1 Number missing: 4, Reason: 394 patients assigned to TAVR. 390 underwent TAVR (reported in Adams paper, 1 additional patient becomes apparent in follow up papers but data is not available for this patient).; Group 2 Number missing: 44, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR (reported in Adams paper, 6 additional patients become apparent in follow up papers but data is not available for this patient).

Protocol outcome 11: Prosthetic valve endocarditis at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Valve endocarditis at 5 years; Group 1: 5/391, Group 2: 5/359; Comments: As-treated results from Gleason 2018 paper.
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34, Reason: 394 patients assigned to TAVR. 391 underwent TAVR. 31

patients in the TAVR group said to have left the study but were included in the as-treated analysis.; Group 2 Number missing: 128, Reason: 401 assigned to undergo SAVR. 359 underwent SAVR. 86 patients in the TAVR group said to have left the study but were included in the as-treated analysis. Protocol outcome 12: Major vascular complications at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): Major vascular complications at 30 days; Group 1: 23/390, Group 2: 6/357 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Reason not provided, reported in appendix; Group 2 Number missing: 44, Reason: Reason not provided, reported in appendix Protocol outcome 13: Renal failure at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): AKI at 2 years; Group 1: 24/394, Group 2: 54/401; Comments: Kaplan Meier estimates Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Only reported at 2 years or beyond. No reference for 30 days.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Onset or exacerbation of heart failure at ≥12 months; Length of hospital stay at after intervention

Study	Ahangar 2013[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in India; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Not clear: Until they left hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Thorough clinical examination, blood tests and imaging (including echocardiography)
Stratum	Mixed/unclear aortic valve disease
Subgroup analysis within study	Not applicable
Inclusion criteria	People requiring aortic valve replacement (type of aortic valve disease unclear)
Exclusion criteria	High risk people (ASA 3 or 4), people with coagulation disorders, previous cardiac surgery, associated coronary artery disease, associated mitral valve disease requiring surgical intervention and those who had not signed written informed consent forms
Recruitment/selection of patients	Conducted with people from one centre who had aortic valve replacement from September 2010 to August 2012
Age, gender and ethnicity	Age - Mean (SD): Intervention: 38.5±10.6, control: 36.6±6.7. Gender (M:F): 20:40. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Childbearing age: Women of childbearing age (<45) (Mean age falls below this range). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear 5. Primary vs

	secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): No systolic dysfunction (Majority had an LVEF of >40%).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves. Right anterolateral thoracotomy - People were positioned supine with the right side elevated to 30 degrees. Usual draping. 35cm incision in the right submammary fold starting at 35cm from the lateral border of the sternum. Entering through the third intercostal space. Duration N/A - surgical procedure. Concurrent medication/care: Same general anaesthetic techniques for both groups. People were electively ventilated for some hours after the completion of surgery. Post extubation support in ITU. IV morphine (3mg QDS) for analgesia. Oral anticoagulation started on the 2nd postop day with acenocoumarol to maintain an INR of 2.0-2.5. IV antibiotics (ceftriaxone/sulbactam and amikacin) administered during the hospital stay. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear (n=30) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Conventional median sternotomy with the person positioned supine. Duration N/A - surgical procedure. Concurrent medication/care: Same general anaesthetic techniques for both groups. People were electively ventilated for some hours after the completion of surgery. Post extubation support in ITU. IV morphine (3mg QDS) for analgesia. Oral anticoagulation started on the 2nd postop day with acenocoumarol to maintain an INR of 2.0-2.5. IV antibiotics (ceftriaxone/sulbactam and amikacin) administered during the hospital stay. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINIMALLY INVASIVE SURGERY REPLACEMENT WITH BIOLOGICAL OR	

MECHANICAL VALVES versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES Protocol outcome 1: Length of hospital stay at after intervention - Actual outcome for Mixed/unclear aortic valve disease: Post-op hospital stay at After procedure; Group 1: mean 6.9 days (SD 1); n=30, Group 2: mean 8 days (SD 1.4); n=30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex was different between groups (intervention: 26.66% male, 73.3% female. Control: 43.33% male, 56.66% female) and otherwise only reports a limited number of factors (age, sex, NYHA class, LVEF); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Intervention-related mortality at 30 days; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Intervention-related major bleeding at 30 days; Need for re-intervention at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study	Aris 1999[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Spain; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Aortic stenosis (mixed bicuspid and non-bicuspid or unclear)
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients undergoing first-time elective, isolated aortic valve replacement
Exclusion criteria	Not stated
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 64±11. Gender (M:F): Not reported. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mean age with SD is just on the 75 years border). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Mixed (Reports operative risk score (not specific score type). Intervention group: 11.6±5, control group: 11.4±5.5). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable

Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Ministernotomy replacement with mechanical valve. Ministernotomy. 13 patients underwent a reversed "L" ministernotomy. 7 underwent a reversed "C" incision. All but 1 patient in the entire study had mechanical prosthesis. Duration N/A - Surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mechanical (n=20) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with mechanical valve. Median sternotomy. All patients but 1 in the entire study had mechanical prosthesis. Duration N/A - Surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mechanical
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPLACEMENT WITH MECHANICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH MECHANICAL VALVE
Protocol outcome 1: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): 30 day mortality at 30 days; Group 1: 1/20, Group 2: 2/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome at less than 3 months, so downgraded for indirectness as per protocol; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): 30 day mortality at 30 days; Group 1: 2/20, Group 2: 2/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Need for re-intervention at ≥12 months - Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Need for re-intervention at 30 days; Group 1: 1/20, Group 2: 0/20; Comments: Surgical drainage of a pericardial effusion Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Length of hospital stay at after intervention - Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Length of hospital stay at 30 days; Group 1: mean 6.3 Days (SD 2.3); n=20, Group 2: mean 6.3 Days (SD 2.4); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Intervention-related atrial fibrillation at 30 days - Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): New-onset atrial fibrillation at 30 days; Group 1: 4/20, Group 2: 2/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Intervention-related major bleeding at 30 days; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study	Arora 1993[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in India; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Mean (SD) follow-up, 22 (6.3) months (range, 6-38 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography pre-intervention
Stratum	Mitral stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic patients with moderate-to-severe mitral stenosis
Exclusion criteria	More than minimal mitral valve calcification; atrial fibrillation; >2+ mitral regurgitation
Recruitment/selection of patients	Consecutive eligible patients
Age, gender and ethnicity	Age - Mean (SD): BMV, 19.4 (5.47); CMV, 19.9 (6.4) years. Gender (M:F): 80/120. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean age ~19 years in both groups). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Morphology suitable for transcatheter intervention (Assumed as transcatheter intervention was one of the randomisation options). 4. Operative risk (for AS and MR): Not applicable 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable

Extra comments	Mean (SD) mitral valve area: 0.85 (0.3) vs. 0.79 (0.2) cm^2; mean (SD) transmitral end-diastolic gradient: 23.35 (5.4) vs. 25.9 (2.78) mmHg; mitral valve calcification: 2% vs. 3%
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Transcatheter repair. Percutaneous balloon mitral valvuloplasty. Performed by transvenous transatrial route with a double-balloon technique. Duration N/A - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Not applicable (Repair procedure rather than replacement). (n=100) Intervention 2: Minimally invasive surgery repair. Surgical closed mitral valvotomy. Performed by lateral thoracic approach with the Tubb's dilator. Duration N/A - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter intervention). 2. Valve type: Not applicable (Repair procedure rather than replacement).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus MINIMALLY INVASIVE SURGERY REPAIR

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral stenosis: Mortality (all-cause) at Mean (SD) follow-up, 22 (6.3) months; Group 1: 2/100, Group 2: 2/100; Comments: All of these events also included in cardiac mortality and intervention-related mortality outcomes. Events included 2 consequent to haemodynamic collapse due to hemopericardium during attempted septal puncture (transcatheter repair group) and 2 in patients with severe pulmonary hypertension who died of persistent low-output state and intractable arrhythmia following surgery.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral stenosis: Mortality (related to cardiac causes) at Mean (SD) follow-up, 22 (6.3) months; Group 1: 2/100, Group 2: 2/100;

Comments: All of these events also included in all-cause mortality and intervention-related mortality outcomes. Events included 2 consequent to haemodynamic collapse due to hemopericardium during attempted septal puncture (transcatheter repair group) and 2 in patients with severe pulmonary hypertension who died of persistent low-output state and intractable arrhythmia following surgery.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Mitral stenosis: Mortality at 30 days - Mean (SD) follow-up, 22 (6.3) months; Group 1: 2/100, Group 2: 2/100; Comments: All of these events also included in all-cause mortality and cardiac mortality outcomes. Events included 2 consequent to haemodynamic collapse due to hemopericardium during attempted septal puncture (transcatheter repair group) and 2 in patients with severe pulmonary hypertension who died of persistent low-output state and intractable arrhythmia following surgery.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Not clear if all within 30 days, but how described appear to be complications of the procedure and occurred during/shortly after intervention; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral stenosis: Cerebrovascular accident at 30 days - mean (SD) follow-up, 22 (6.3) months; Group 1: 0/98, Group 2: 0/98; Comments: 2 deaths in each group so missing data for these patients in terms of stroke outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: No indirectness based on follow-up as zero events in each arm means at 30 days also zero events for both; Group 1 Number missing: 2, Reason: 2 deaths that appear to be within 30 day time-point (intra/postoperative deaths); Group 2 Number missing: 2, Reason: 2 deaths that appear to be within 30 day time-point (intra/postoperative deaths)

Protocol outcome 5: Intervention-related major bleeding at 30 days
- Actual outcome for Mitral stenosis: Excessive bleeding from the site of venous puncture or thoracotomy at 30 days - mean (SD) follow-up, 22 (6.3) months; Group 1: 0/98, Group 2: 0/98; Comments: 2 deaths in each group so missing data for these patients in terms of this outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: No indirectness based on follow-up as zero events in each arm means at 30 days also zero events for both; Group 1 Number missing: 2, Reason: 2 deaths that appear to be within 30 day time-point (intra/postoperative deaths); Group 2 Number missing: 2, Reason: 2 deaths that appear to be within 30 day time-point (intra/postoperative deaths)

Protocol outcome 6: Major vascular complications at 30 days - Actual outcome for Mitral stenosis: Procedure-induced atrial septal perforation at 30 days - Intra/postoperative; Group 1: 8/100, Group 2: 0/100; Comments: Potentially missing data for some that died before this outcome could develop, but unclear as does not state whether any that died experienced this before death. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Need for re-intervention at ≥12 months; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Renal failure at 30 days

Study	Ben Farhat 1998[49]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Tunisia; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Up to 7 years follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Doppler echocardiography
Stratum	Mitral stenosis: All with severe pliable mitral stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	rheumatic, severe right mitral stenosis (mitral valve area ≤1.3 cm^2)
Exclusion criteria	Presence of other cardiac valvular disease; history of thromboembolism; mitral valve calcifications on fluoroscopy and two-dimensional echocardiography; left atrium thrombus on transthoracic echocardiography
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): balloon commissurotomy, 29 (12) years; open commissurotomy, 27 (9) years; closed commissurotomy, 28 (10) years. Gender (M:F): balloon commissurotomy, 7/23; open commissurotomy, 9/21; closed commissurotomy, 7/23. Ethnicity: Not reported

Further population details	1. Age: <75 years (Mean age in both groups was <75 years). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Morphology suitable for transcatheter intervention (Assumed as percutaneous/transcatheter repair was one of the randomised interventions). 4. Operative risk (for AS and MR): Not applicable 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Extra comments	Study notes that results may be because of younger age of patients compared with other studies and general population. They also note all had favourable mitral valve anatomy as patients with calcifications or severe subvalvular disease were excluded. All had pliable valves with an echo score ≤8/16. Patients with atrial fibrillation and those with severe pulmonary hypertension or mild-to-moderate tricuspid regurgitation were not excluded. NYHA class: II (10 vs. 13 vs. 10%), III (70 vs. 67 vs. 73%) and IV (20 vs. 20 vs. 17%); mean (SD) pressure variables: right atrial [4.8 (1.4) vs. 5.0 (1.4) vs. 4.6 (1.3) mmHg], systolic pulmonary artery [52 (21) vs. 51 (25) vs. 49 (23) mmHg], pulmonary artery [38 (12) vs. 36 (11) vs. 35 (11) mmHg] and pulmonary wedge [26 (7) vs. 25 (7) vs. 24 (8) mmHg]; mean (SD) mitral valve gradient, 21 (8) vs. 20 (8) vs. 19 (7); mean (SD) mitral valve area, 0.9 (0.2) vs. 0.9 (0.2) vs. 0.9 (0.2) cm^2; mean (SD) cardiac index, 3.1 (0.5) vs. 3.0 (0.7) vs. 3.2 (0.8) L•min-1•m-2; rhythm: sinus (77 vs. 73 vs. 74%) and atrial fibrillation (23 vs. 27 vs. 27%); mean (SD) echocardiographic score, 6.0 (1.0) vs. 6.0 (1.0) vs. 6.1 (1.1)
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Transcatheter repair. Balloon mitral commissurotomy. Performed using two pigtail balloons Triad AT catheters through a single interatrial septum puncture. Balloons ranging in size from 15-20 mm selected according to patient body surface area and the diameter of the mitral annulus. Larger balloons were used in 4 patients with immediate unsatisfactory results to redilate the mitral orifice. Duration N/A - surgical procedure. Concurrent medication/care: Before and after mitral commissurotomy, all underwent right- and left-sided heart catheterisation at rest. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Not applicable (Repair procedure rather than replacement). (n=30) Intervention 2: Standard surgery repair - Median sternotomy - repair. Open mitral commissurotomy. Performed through a median sternotomy. Both commissures were incised in all patients. Both papillary

	muscles were split in 12 patients and only the posterior muscle was split in 2 patients. One or two stitches of suture were placed across one or both commissures in 16 cases. Duration N/A - surgical procedure. Concurrent medication/care: Before and after mitral commissurotomy, all underwent right- and left-sided heart catheterisation at rest. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter procedure). 2. Valve type: Not applicable (Repair procedure rather than replacement). (n=30) Intervention 3: Minimally invasive surgery repair. Closed mitral commissurotomy performed through a left lateral thoracotomy using a Tubb's dilator in 14 patients and a Dubost dilator in 16 patients. Both commissures could be properly opened in 20 cases. Duration N/A - surgical procedure. Concurrent medication/care: Before and after mitral commissurotomy, all underwent right- and left-sided heart catheterisation at rest. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter procedure). 2. Valve type: Not applicable (Repair procedure rather than replacement).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus MEDIAN STERNOTOMY - REPAIR

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 7 years; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 7 years; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Mitral stenosis: Deaths at 30 days; Group 1: 0/30, Group 2: 0/30

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: Doesn't report at 30 days but as zero events at 7 years can deduce none at 30 days; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral stenosis: Systemic thromboembolism at 30 days; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Doesn't report at 30 days but as zero events at 7 years can deduce none at 30 days. Indirectness as not limited to stroke/TIA; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Need for re-intervention at ≥12 months
- Actual outcome for Mitral stenosis: Reintervention (includes repair and replacement procedures) at 7 years; Group 1: 3/30, Group 2: 2/30; Comments: Transcatheter: 2 underwent balloon mitral commissurotomy due to restenosis and 1 underwent replacement due to grade 3 MR. Median sternotomy: 2 underwent balloon mitral commissurotomy due to restenosis.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus MINIMALLY INVASIVE SURGERY REPAIR (LEFT LATERAL THORACTOMY)

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 7 years; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 7 years; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Mitral stenosis: Deaths at 30 days; Group 1: 0/30, Group 2: 0/30

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: Doesn't report at 30 days but as zero events at 7 years can deduce none at 30 days; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral stenosis: Systemic thromboembolism at 30 days; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Doesn't report at 30 days but as zero events at 7 years can deduce none at 30 days. Indirectness as not limited to stroke/TIA; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Need for re-intervention at ≥12 months
- Actual outcome for Mitral stenosis: Reintervention (includes repair and replacement procedures) at 7 years; Group 1: 3/30, Group 2: 15/30; Comments: Transcatheter: 2 underwent balloon mitral commissurotomy due to restenosis and 1 underwent replacement due to grade 3 MR. Minimally invasive: 13 underwent balloon mitral commissurotomy and 2 underwent replacement due to either residual stenosis or restenosis - those that underwent replacement had associated grade 2 MR.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINIMALLY INVASIVE SURGERY REPAIR (LEFT LATERAL THORACTOMY) versus MEDIAN STERNOTOMY - REPAIR

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 7 years; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 7 years; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related mortality at 30 days

- Actual outcome for Mitral stenosis: Deaths at 30 days; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: Doesn't report at 30 days but as zero events at 7 years can deduce none at 30 days; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Intervention-related stroke or TIA at 30 days - Actual outcome for Mitral stenosis: Systemic thromboembolism at 30 days; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Doesn't report at 30 days but as zero events at 7 years can deduce none at 30 days. Indirectness as not limited to stroke/TIA; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Need for re-intervention at ≥12 months - Actual outcome for Mitral stenosis: Reintervention (includes repair and replacement procedures) at 7 years; Group 1: 15/30, Group 2: 2/30; Comments: Minimally invasive: 13 underwent balloon mitral commissurotomy and 2 underwent replacement due to either residual stenosis or restenosis - those that underwent replacement had associated grade 2 MR. Median sternotomy: 2 underwent balloon mitral commissurotomy due to restenosis. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related major bleeding at 30 days; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study	Bogachev-Prokophiev 2017[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=88)
Countries and setting	Conducted in Russia; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Up to 24 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Abnormalities of mitral valve apparatus revealed by echocardiography and cardiac magnetic resonance imaging with presence of severe mitral regurgitation
Stratum	Mitral regurgitation: All with severe mitral regurgitation in addition to hypertrophic obstructive cardiomyopathy
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults aged ≥18 years with hypertrophic obstructive cardiomyopathy who met the indications for operation according to the guidelines of the European Society of Cardiology; septum thickness ≥15 mm measured by echocardiography and/or cardiac magnetic resonance imaging; instantaneous peak Doppler LVOT pressure gradient ≥50 mmHg at rest; abnormalities of the MV apatus, such as papillary hypertrophy and displacement, fibrotic and retracted secondary chordae, degenerative lesions, etc. revealed by echo and cardiac magnetic resonance imaging; resting systolic anterior motion; severe mitral regurgitation
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive patients with severe mitral regurgitation and hypertrophic obstructive cardiomyopathy referred for septal myectomy

Age, gender and ethnicity	Age - Mean (SD): Replacement, 50.8 (14.3) years; repair, 48.3 (14.2) years. Gender (M:F): Replacement, 20/27; repair, 13/28. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean age in both groups <75 years). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Low (Mean EuroSCORE II <4% in both groups). 5. Primary vs secondary valve disease (for MR and TR): Not stated / Unclear (Unclear but could be secondary as present alongside hypertrophic obstructive cardiomyopathy). 6. Systolic dysfunction (for AR): Not applicable
Extra comments	. Mean (SD) BMI, 29.3 (5.9) vs. 30.5 (5.8) kg/m²; syncope, 29.8 vs. 29.3%; NYHA class II (25.5 vs. 22.0%), III (70.2 vs. 70.7%) and IV (2.1 vs. 7.3%); beta-blockers, 29.7 vs. 36.6%; verapamil, 6.4 vs. 4.9%; disopyramide, 8.5 vs. 4.9%; thiazide diuretics, 25.5 vs. 36.6%; mean (SD) resting left ventricular outflow tract gradient, 90.2 (21.2) vs. 95.3 (27.8) mmHg; mean (SD) septum thickness, 25.5 (4.3) vs. 26.8 (4.3) mm; moderate renal impairment, 10.6 vs. 4.9%; hypertension, 40.4 vs. 51.2%; atrial fibrillation, 12.8 vs. 12.2%; mean (SD) 5-year risk of sudden cardiac death, 5.4 (0.7) vs. 5.2 (0.8)%; previous alcohol septal ablation therapy, 17.0 vs. 14.6%; mean (SD) EuroSCORE II, 1.8 (0.4) vs. 1.7 (0.3)%
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Surgical replacement with biological or mechanical valve (unclear/mixed invasiveness). Surgical replacement (unclear whether standard or minimally invasive). Real-time transoesophageal echocardiography (TOE) was performed after induction of anaesthesia for mitral valve lesion estimation and modelling of an adequate length and depth of resection into the left ventricular outflow tract (LVOT). The aorta was cross-clamped and cold crystalloid cardioplegic solution was used for myocardial protection with antegrade root flow. Posterior leaflet was preserved and On-X prostheses implanted in the intra-annular position using U-stitches with pledgets in anatomic orientation with a 45° rotation about the left ventricular long axis. Control TOE was performed after withdrawal of bypass for routine assessment of LVOT haemodynamics. Direct transaortic catheterization was used for the measurement of pressure gradients. Cardiopulmonary bypass was re-established if there was residual moderate-to-severe mitral regurgitation or if a ventricular septal defect was observed. Duration Not reported. Concurrent medication/care: A transverse aortotomy approach for extended septal myectomy was used in all cases. Patients who received a mechanical mitral valve were kept on lifelong anticoagulation

	with an international normalized ratio target in the range of 2.5–3.5. Concomitant procedures included maze IV for atrial fibrillation and coronary artery bypass grafting. Indirectness: Serious indirectness; Indirectness comment: Unclear invasiveness of procedure (standard or minimally invasive) Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mechanical (On-X prostheses). Comments: The inclusion criterion for participating surgeons was experience of at least 30 septal procedures per year (2 surgeons). (n=44) Intervention 2: Surgical repair (unclear/mixed invasiveness). Surgical repair (unclear whether standard or minimally invasive). Real-time transoesophageal echocardiography (TOE) was performed after induction of anaesthesia for mitral valve lesion estimation and modelling of an adequate length and depth of resection into the left ventricular outflow tract (LVOT). The aorta was cross-clamped and cold crystalloid cardioplegic solution was used for myocardial protection with antegrade root flow. For repair, transaortic subvalvular apparatus interventions performed, including retracted secondary chordae cutting and abnormal papillary muscle release and/or resection . Duration Not reported. Concurrent medication/care: A transverse aortotomy approach for extended septal myectomy was used in all cases. Low-dose aspirin was prescribed postoperatively in the repair group for patients who were in sinus rhythm, as documented by 24-h Holter monitoring. Concomitant procedures included maze IV for atrial fibrillation and coronary artery bypass grafting. Indirectness: Serious indirectness; Indirectness comment: Unclear invasiveness of procedure (standard or minimally invasive) Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not applicable Comments: The inclusion criterion for participating surgeons was experience of at least 30 septal procedures per year (2 surgeons).
Funding	Academic or government funding (Supported by a grant from the President of the Russian Federation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SURGICAL REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES (UNCLEAR/MIXED INVASIVENESS) versus SURGICAL REPAIR (UNCLEAR/MIXED INVASIVENESS) Protocol outcome 1: All-cause mortality at ≥12 months	

- Actual outcome for Mitral regurgitation: Mortality (all-cause) at 24 months; Group 1: 8/47, Group 2: 1/41; Comments: Note 3 initially failing repair were crossed over into replacement group for analysis.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for groups as-treated - differences for certain factors such as % with hypertension.; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Three switched after failing initial repair procedure into the replacement group.
- Actual outcome for Mitral regurgitation: Mortality (all-cause) at 24 months; Group 1: Observed events 8 n=47 ; Group 2: Observed events 1 n=41; HR 4.12; Lower CI 1.11 to Upper CI 15.28; Log rank variance: 2.24; Log rank observed minus expected events: 3.17; Test statistic: 0.034; Advantage to research or control? Control; Follow up details: All followed up to 24 months; Comments: Logrank variance and O-E calculated using P-value, total events and numbers analysed in each arm. Note 3 initially failing repair were crossed over into replacement group for analysis.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for groups as-treated - differences for certain factors such as % with hypertension.; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Three switched after failing initial repair procedure into the replacement group.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral regurgitation: Mortality (due to cardiac causes) at 24 months; Group 1: 8/47, Group 2: 1/41; Comments: Note 3 initially failing repair were crossed over into replacement group for analysis. All deaths in study were cardiac-related. Deaths in replacement group include 1 due to valve-related thromboembolic event, 3 due to severe pulmonary oedema as a result of prosthesis thrombosis, 2 due to fatal thromboembolic complications and 2 sudden cardiac deaths. The death in the repair group was sudden cardiac death.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for groups as-treated - differences for certain factors such as % with hypertension.; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Three switched after failing initial repair procedure into the replacement group.

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Mitral regurgitation: Mortality at 30 days; Group 1: 1/47, Group 2: 0/41; Comments: Note 3 initially failing repair were crossed over into replacement group for analysis. 1 death in replacement group on 20th day after surgery due to valve-related thromboembolic event (stroke)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for groups as-treated - differences for certain factors such as % with hypertension.; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Three switched after failing initial repair procedure into the replacement group.

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral regurgitation: Stroke at 30 days; Group 1: 1/47, Group 2: 0/41; Comments: Note 3 initially failing repair were crossed over into replacement group for analysis. 1 stroke in replacement group on 20th day after surgery due to a valve-related thromboembolic event. This patient died as a result and is included in the 30-day mortality outcome.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for groups as-treated - differences for certain factors such as % with hypertension.; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Three switched after failing initial repair procedure into the replacement group.

Protocol outcome 5: Intervention-related major bleeding at 30 days
- Actual outcome for Mitral regurgitation: Bleeding at Postoperative; Group 1: 1/47, Group 2: 0/41; Comments: Note 3 initially failing repair were crossed over into replacement group for analysis. Bleeding was due to left ventricular free wall rupture and required intensive care unit admission and emergency repair.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline details for groups as-treated - differences for certain factors such as % with hypertension.; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Three switched after failing initial repair procedure into the replacement group.

Protocol outcome 6: Need for re-intervention at ≥12 months
- Actual outcome for Mitral regurgitation: Reoperation at 24 months; Group 1: 0/44, Group 2: 3/44; Comments: Reports as randomised. Those with events in repair group were subsequently crossed over to receive replacement and were analysed in new groups for all other outcomes.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline details for groups as-treated, rather than as-randomised, given in paper.; Blinding details: Could have been subjective decision by surgeon based on knowledge of intervention received; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 7: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Mitral regurgitation: Permanent dual-chamber pacemaker implantation at Early postoperative period; Group 1: 3/47, Group 2: 2/41; Comments: Note 3 initially failing repair were crossed over into replacement group for analysis. Pacemaker implanted prior to discharge due to complete heart block following extended myectomy.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for groups as-treated - differences for certain factors such as % with hypertension.; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Three switched after failing initial repair procedure into the replacement group. Protocol outcome 8: Major vascular complications at 30 days - Actual outcome for Mitral regurgitation: Surgical complications (those appearing to be vascular based on VARC-2) at Intraoperative; Group 1: 1/47, Group 2: 1/41; Comments: Note 3 initially failing repair were crossed over into replacement group for analysis. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for groups as-treated - differences for certain factors such as % with hypertension.; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Three switched after failing initial repair procedure into the replacement group.	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Renal failure at 30 days

Study	Bonacchi 2002[58]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Not clear: Until end of hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Mixed/unclear aortic valve disease
Subgroup analysis within study	Not applicable
Inclusion criteria	People with aortic valve pathology who underwent aortic valve replacement
Exclusion criteria	People undergoing emergency operations or concomitant coronary revascularisation, people with depressed left ventricular function (LVEF <0.25) and people with a heavily calcified ascending aorta.
Recruitment/selection of patients	Consecutive people with aortic valve pathology who underwent elective aortic valve replacement
Age, gender and ethnicity	Age - Mean (SD): Intervention: 62.6±9.5, Control: 64±12.4. Gender (M:F): Sex not stated. Ethnicity: Not stated
Further population details	1. Age: Mixed (Mean age Intervention: 62.6±9.5, mean age control: 64±12.4). 2. Childbearing age: Women not of childbearing age (≥45 years) (Based on mean age). 3. Morphology (for MS): Not applicable 4.

	Operative risk (for AS and MR): Not stated / Unclear 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): No systolic dysfunction
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves. Ministernotomy - Reversed-C in 15 people, reversed-L in 25 people. Using a 6-10cm midline skin incision starting at the right border of the fourth-to-fifth intercostal space. Duration N/A - surgical procedure. Concurrent medication/care: Same anaesthetic regime and care used between groups. Specifics concomitant treatment not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear (n=40) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. A midline skin incision, 20-25cm long, from the sternal notch to the xiphoid appendage. Duration N/A - surgical procedure. Concurrent medication/care: Same anaesthetic regime and care used between groups. Specifics concomitant treatment not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINIMALLY INVASIVE SURGERY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: Intervention-related mortality at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: In-hospital death at During hospital admission; Group 1: 1/40, Group 2: 2/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age and NYHA class. Does not state sex. States that a number of other factors are significant but doesn't state the values.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Intervention-related major bleeding at 30 days - Actual outcome for Mixed/unclear aortic valve disease: Reexploration for bleeding at During hospital admission; Group 1: 0/40, Group 2: 3/40 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age and NYHA class. Does not state sex. States that a number of other factors are significant but doesn't state the values.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay at after intervention - Actual outcome for Mixed/unclear aortic valve disease: Hospital stay at During hospital admission; Group 1: mean 7.2 days (SD 1.6); n=40, Group 2: mean 8.2 days (SD 2.3); n=40 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age and NYHA class. Does not state sex. States that a number of other factors are significant but doesn't state the values.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Intervention-related atrial fibrillation at 30 days - Actual outcome for Mixed/unclear aortic valve disease: Atrial fibrillation at During hospital admission; Group 1: 4/40, Group 2: 3/40 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age and NYHA class. Does not state sex. States that a number of other factors are significant but doesn't state the values.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Need for re-intervention at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study (subsidiary papers)	CADENCE-MIS trial: Borger 2015[60] (Borger 2016[59])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Germany; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Preoperative investigations (not stating the type) with previous diagnosis
Stratum	Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Includes patients with bicuspid aortic valve (Sievers 1). Intervention: 19 (41%), Control: 17 (35%).
Subgroup analysis within study	Not applicable
Inclusion criteria	Isolated aortic valve surgery for aortic stenosis with or without aortic insufficiency, low-to-moderate surgical risk (i.e. logistic EuroScore <20) and NYHA class II or greater.
Exclusion criteria	Pure aortic insufficiency, planned concomitant procedures, previous cardiac surgery, true bicuspid aortic valve, ejection fraction of <25%, and recent myocardial infarction or stroke.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Intervention: 73.0±5.3, Control: 74.2±5.0. Gender (M:F): 48:46. Ethnicity: Not stated
Further population details	1. Age: Mixed (Mean age intervention: 73.0±5.3, control: 74.2±5.0. Confidence intervals fall on both sides of the 75 year limit.). 2. Childbearing age: Women not of childbearing age (≥45 years) (Taken by mean age

	being >45 years.). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Mixed (Low-to-moderate. Logistic EuroSCORE intervention: 6.4±3.7, Logistic EuroSCORE control: 6.7±3.6, EuroSCOREII intervention: 38: 1.7±0.9, EuroSCOREII control: 40: 1.8±1.0, STS score intervention: 1.6±0.7 (?missing number), STS score control: 47: 1.7±0). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Extra comments	. Any population values are taken from as treated numbers, total number of patients in this are 94. No reported values are present for the other patients randomised who were not included in the final analysis.
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Ministernotomy replacement with biological valve. Upper hemisternotomy into the third or fourth intercostal space. Duration N/A - Surgical procedure. Concurrent medication/care: None stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological (n=49) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological valve. Median sternotomy. Duration N/A - Surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological
Funding	Study funded by industry (Edwards Lifesciences LLC)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPLACEMENT WITH BIOLOGICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL VALVE

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Mortality at 1 year; Group 1: 4/49, Group 2: 3/48; Comments:

Intervention group: 1 death due to cardiogenic shock, 1 due to pericardial tamponade, 1 due to pneumonia and sepsis. The study excludes 1 death, that has been included in the ITT group (patient died from multisystem organ failure secondary to right heart failure and low cardiac output after inability to site the valve during the minimally invasive procedure leading to a tear in the aortic annulus before switching to a switching to a minimally invasive approach with a different valve type). Control group: 2 due to unknown reasons (1 at 15 days postop, the other at 202) and 1 due to major neurological bleeding.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 2, Reason: 2 patients excluded because of intraoperative screening failure; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Mortality at 1 year; Group 1: 3/49, Group 2: 0/48; Comments: Intervention group: 1 death due to cardiogenic shock, 1 due to pericardial tamponade. The study excludes 1 death, that has been included in the ITT group (patient died from multisystem organ failure secondary to right heart failure and low cardiac output after inability to site the valve during the minimally invasive procedure leading to a tear in the aortic annulus before switching to a minimally invasive approach with a different valve type). Control group: 2 due to unknown reasons (1 at 15 days postop, the other at 202) - these were not included in this due to the reason being unknown.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 2, Reason: 2 patients excluded because of intraoperative screening failure ; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Mortality at 30 days; Group 1: 3/49, Group 2: 1/48; Comments: Intervention
group: 1 death due to cardiogenic shock, 1 due to pericardial tamponade. The study excludes 1 death, that has been included in
the ITT group (patient died from multisystem organ failure secondary to right
heart failure and low cardiac output after inability to site the valve during
the minimally invasive procedure leading to a tear in the aortic annulus before
switching to a minimally invasive approach with a different valve type).
Control group: 1 due to unknown reasons (1 at 15 days postop).

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 2, Reason: 2 patients excluded because of intraoperative screening failure ; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): EQ-5D at 3 months; Group 1: mean 0.9 (SD 0.1); n=46, Group 2: mean 0.9 (SD 0.1); n=48; EQ-5D 0-1 Top=High is good outcome; Comments: Reported: Baseline intervention: 0.9±0.1, Baseline control: 0.9±0.1, 3 month intervention: 0.9±0.1, 3 month control: 0.9±0.1,
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 5, Reason: 2 patients excluded because of intraoperative screening failure. 3 patients excluded due to change of procedure to a non-study valve type (still a bioprosthetic valve. ; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Cerebrovascular accident at 30 days; Group 1: 2/46, Group 2: 1/48
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 5, Reason: 2 patients excluded because of intraoperative screening failure. 3 patients excluded due to change of procedure to a non-study valve type (still a bioprosthetic valve. ; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.

Protocol outcome 6: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Major bleeding at 30 days; Group 1: 3/46, Group 2: 4/48
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 5, Reason: 2 patients excluded because of intraoperative screening failure. 3 patients

excluded due to change of procedure to a non-study valve type (still a bioprosthetic valve. ; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.

Protocol outcome 7: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Reoperation at 30 days; Group 1: 1/46, Group 2: 1/48
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 5, Reason: 2 patients excluded because of intraoperative screening failure. 3 patients excluded due to change of procedure to a non-study valve type (still a bioprosthetic valve. ; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.

Protocol outcome 8: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): New pacemaker at 30 days; Group 1: 2/46, Group 2: 0/48
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 5, Reason: 2 patients excluded because of intraoperative screening failure. 3 patients excluded due to change of procedure to a non-study valve type (still a bioprosthetic valve. ; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.

Protocol outcome 9: Prosthetic valve endocarditis at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Endocarditis at 1 year; Group 1: 0/46, Group 2: 0/48
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 5, Reason: 2 patients excluded because of intraoperative screening failure. 3 patients excluded due to change of procedure to a non-study valve type (still a bioprosthetic valve. ; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.

Protocol outcome 10: Renal failure at 30 days

- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Renal failure at 30 days; Group 1: 2/46, Group 2: 0/48 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Various outcomes with differences (sex, number of obese patients, number of patients at NYHA class >=3, hypercholesterolaemia, smoking history, diabetes, liver disease). Generally the intervention group seems to have poorer health outcomes before the procedure.; Group 1 Number missing: 5, Reason: 2 patients excluded because of intraoperative screening failure. 3 patients excluded due to change of procedure to a non-study valve type (still a bioprosthetic valve. ; Group 2 Number missing: 1, Reason: 1 patient withdrew from the study.	
Protocol outcomes not reported by the study	Onset or exacerbation of heart failure at ≥12 months; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related atrial fibrillation at 30 days; Major vascular complications at 30 days

Study	Calderon 2009[68]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in France; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Aortic stenosis (mixed bicuspid and non-bicuspid or unclear)
Subgroup analysis within study	Not applicable
Inclusion criteria	Any patient over 18 years old, strictly less than or equal to ASA 3, providing informed signed consent, and having left ventricular ejection fraction above 40%
Exclusion criteria	Redo, combined surgery, ASA score more than or equal to 4, acute pulmonary oedema, chronic obstructive pulmonary disease (COPD), endocarditis, chronic renal failure, antiplatelet discontinuation less than 7 days before surgery, and no known hemostatic abnormality
Age, gender and ethnicity	Age - Mean (SD): Intervention group: 70.9±11.4, Control group: 70.8±10.2. Gender (M:F): 50:28. Ethnicity: Not stated
Further population details	1. Age: Mixed (Mean age with confidence interval crosses 75 years). 2. Childbearing age: Women not of childbearing age (≥45 years) (Assumed from mean age). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Low (Stated in results section. EuroSCORE intervention: 5.4±1.9, EuroSCORE control:

	5.2±1.8). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Ministernotomy replacement with biological or mechanical valve. Reversed-L sternal incision. Does not state the type of valve used during the replacement. Duration N/A - surgical procedure. Concurrent medication/care: Postoperative analgesia with PCA morphine, IV paracetamol and ketoprofen if insufficient relief. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear (Does not state the type of valve used during the replacement.). (n=39) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Standard sternotomy. Does not state the type of valve used during the replacement. Duration N/A - surgical procedure. Concurrent medication/care: Postoperative analgesia with PCA morphine, IV paracetamol and ketoprofen if insufficient relief. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (Does not state the type of valve used during the replacement.).
Funding	Academic or government funding (Supported by the University hospital of Bordeaux and the French Ministry of Research (PHRC program))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES
Protocol outcome 1: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Intervention related mortality at 7 days; Group 1: 0/38, Group 2: 0/39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome at less than 3 months, so downgraded for indirectness as per protocol; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Intervention related mortality at 7 days; Group 1: 0/38, Group 2: 1/39; Comments: Lethal multiorgan failure
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Postoperative bleeding requiring reintervention at 7 days; Group 1: 0/38, Group 2: 1/39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Patients transfused with red blood cells at 7 days; Group 1: 18/38, Group 2: 20/39
Risk of bias: All domain - ; Indirectness of outcome: Serious indirectness

Protocol outcome 4: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Need for re-intervention at 7 days; Group 1: 0/38, Group 2: 2/39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome at less than 3 months, so downgraded for indirectness as per protocol; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Length of hospital stay at after intervention
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Hospital stay at 7 days; Group 1: mean 6 Days (SD 0.32); n=38, Group 2: mean 6.18 Days (SD 1.5); n=39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study (subsidiary papers)	Cardoso 2002[74] (Cardoso 2004[73])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Brazil; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Up to 24 month follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography and ECG at baseline
Stratum	Mitral stenosis: All with tight and pliable mitral stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	NYHA functional class ≥II; echocardiographic score ≤9; age ≤60 years; absent or mild mitral regurgitation
Exclusion criteria	Intracavitary thrombus identified by transthoracic Doppler echocardiography; other cardiac disease requiring surgical correction; previous commissurotomy; previous embolic events
Recruitment/selection of patients	Consecutive patients between December 1989 and April 1994
Age, gender and ethnicity	Age - Mean (SD): Balloon valvuloplasty, 32 (9) years; commissurotomy, 33 (8) years. Gender (M:F): Balloon valvuloplasty, 3/37; commissurotomy, 5/35. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean age in both groups <75 years). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Morphology suitable for transcatheter intervention (Assumed as one of the randomised interventions was percutaneous/transcatheter repair). 4. Operative risk (for AS and MR): Not

	applicable 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Extra comments	NYHA functional class: II (12.5 vs. 7.5%) and III/IV (87.5 vs. 92.5%); cardiac rhythm: sinus rhythm (97.5 vs. 92.5%) and atrial fibrillation (2.5 vs. 7.5%); echocardiographic score: 4/5 (15 vs. 10%), 6/7/8, (77.5 vs. 82.5%) and 9 (7.5 vs. 7.5%); mean (SD) mitral gradient, 11.1 (5.8) vs. 11.7 (5.5) mmHg; mean (SD) mitral valve area, 1.04 (0.23) vs. 0.96 (0.20) cm^2
Indirectness of population	Serious indirectness: Balloon valvuloplasty group includes at least one participant <18 years of age.
Interventions	(n=40) Intervention 1: Transcatheter repair. Percutaneous balloon valvuloplasty performed through the transseptal route by the same interventional cardiologist who had performed the procedure at least 100 times. Double balloon catheter was used in 4 patients. In 7 patients the mitral valve was dilated by a bifoil balloon catheter. Procedure was performed in most patients by the Inoue technique. The procedure was considered effective when full expansion of the balloon was associated with an important decrease in the mitral gradient without detection of substantial mitral regurgitation or mechanical complications. Duration N/A - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Not applicable (Repair procedure rather than replacement). (n=40) Intervention 2: Surgical repair (unclear/mixed invasiveness). Open surgical mitral commissurotomy with cardiopulmonary bypass surgery performed by the same surgeon. Heart was approached through median or right thoracotomy. Myocardial protection consisted of moderate hypothermia (28°C) and crystalloid cardioplegia. Anterior and posterior commissurotomy plus papillarotomy were performed in all patients. Duration N/A - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Surgical procedure not transcatheter). 2. Valve type: Not applicable (Repair procedure rather than replacement).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus SURGICAL REPAIR (UNCLEAR/MIXED INVASIVENESS)

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 24 months; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Details only given for a limited number of factors; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 24 months; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Details only given for a limited number of factors; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Mitral stenosis: Deaths at 30 days; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Details only given for a limited number of factors; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related major bleeding at 30 days
- Actual outcome for Mitral stenosis: Severe bleeding at Postoperative; Group 1: 0/40, Group 2: 5/40; Comments: Treated by blood transfusion for n=4 and by reoperation for n=1
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Time-point measured at unclear but appears to be immediate postoperative complications; Baseline details: Details only given for a limited number of factors; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Need for re-intervention at ≥12 months
- Actual outcome for Mitral stenosis: Re-intervention on valve at 24 months; Group 1: 0/40, Group 2: 0/40

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Details only given for a limited number of factors; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Intervention-related pacemaker implantation at 30 days - Actual outcome for Mitral stenosis: Temporary pacemaker at Postoperative; Group 1: 0/40, Group 2: 2/40; Comments: Both cases were junctional bradycardia requiring temporary pacemaker Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Time-point measured at unclear but appears to be immediate postoperative complications. ; Baseline details: Details only given for a limited number of factors; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 7: Intervention-related atrial fibrillation at 30 days - Actual outcome for Mitral stenosis: Acute atrial fibrillation at Postoperative; Group 1: 0/40, Group 2: 6/40 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Time-point measured at unclear but appears to be immediate postoperative complications. Some patients in each group had atrial fibrillation at baseline and unclear if all events were new-onset in those that didn't have it at baseline.; Baseline details: Details only given for a limited number of factors; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 8: Major vascular complications at 30 days - Actual outcome for Mitral stenosis: Right atrium perforation at Postoperative; Group 1: 2/40, Group 2: 0/40 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Time-point measured at unclear but appears to be immediate postoperative complications. Unclear if intervention required.; Baseline details: Details only given for a limited number of factors; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Prosthetic valve endocarditis at ≥12 months; Renal failure at 30 days

Study (subsidiary papers)	CMILE trial: Dalén 2018[88] (Hashemi 2018[156])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Sweden; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 40 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography before surgery
Stratum	Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Patients with aortic stenosis - not stated whether they had bicuspid or non-bicuspid disease
Subgroup analysis within study	Not applicable:
Inclusion criteria	Adult patients with severe symptomatic aortic stenosis, sinus rhythm and the ability to provide written informed consent
Exclusion criteria	Participation in other trials, left ventricular ejection fraction <45%, presence of any coexisting severe valvular disorder, previous cardiac surgery or urgent surgery
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 68.6 (8.5). Gender (M:F): 25:15. Ethnicity: Not stated
Further population details	1. Age: Mixed (Mean age 68.6 (8.5). Therefore, the SD could go into either subgroup.). 2. Childbearing age: Women not of childbearing age (≥45 years) (Based on mean age being 68.6 (8.5).). 3. Morphology (for MS):

	Not applicable 4. Operative risk (for AS and MR): Low (EuroSCORE II mean (SD) of 1.35 (0.79). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Ministernotomy replacement with biological or mechanical valve. Using partial J-shaped ministernotomy to the third intercostal space. In both procedures the aortic annulus was completely decalcified. Duration N/A - Surgical procedure. Concurrent medication/care: None stated. 4 patients had insulin dependent diabetes mellitus. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (14 patients had biological valves implanted. 5 (26%) patients had mechanical valves implanted.). (n=20) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Median sternotomy. Conventional surgery. In both procedures the aortic annulus was completely decalcified. Duration N/A - Surgical procedure. Concurrent medication/care: None stated. 2 patients had insulin dependent diabetes mellitus. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (16 patients had biological valve replacement. 5 (24%) have mechanical valve replacement.).
Funding	Academic or government funding (Donation by Fredrik Lundberg. The principle author was supported by the Hirsch Fellowship.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: Cardiac mortality at ≥12 months

- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Death at 30 days; Group 1: 0/19, Group 2: 0/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: At <3 months. Therefore, downgraded for indirectness as per protocol; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Death at 30 days; Group 1: 0/21, Group 2: 2/19; Comments: 1 death from aspiration following ileus. 1 death from haemorrhagic pancreatitis.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Stroke and TIA (reported separately) at 30 days; Group 1: 1/19, Group 2: 0/21; Comments: 1 TIA
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Reoperation due to bleeding at 30 days; Group 1: 1/19, Group 2: 1/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Only reports whether bleeding was severe enough to require reoperation. Does not discuss other types of bleeding.; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0

Protocol outcome 5: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Pericardiocentesis within 30 days at 30 days; Group 1: 1/19, Group 2: 1/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group

(1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Reoperation due to bleeding at 30 days; Group 1: 1/19, Group 2: 1/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Reoperation for paravalvular regurgitation at 30 days; Group 1: 0/19, Group 2: 0/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0

Protocol outcome 6: Length of hospital stay at after intervention
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): In-hospital stay at 30 days;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0

Protocol outcome 7: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): De novo pacemaker at 30 days; Group 1: 1/19, Group 2: 2/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0

Protocol outcome 8: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): New-onset atrial fibrillation at 30 days; Group 1: 7/19, Group 2: 6/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0

Protocol outcome 9: Renal failure at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Postoperative dialysis at 30 days; Group 1: 1/21, Group 2: 1/19
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Baseline details: Ministernotomy group has a lower surgical risk (1.26 (0.65)) than the sternotomy group (1.44 (0.90)). Unsure if this is significant.; Group 1 Number missing: 1, Reason: Switched to control group intraoperatively; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Re-hospitalisation at ≥12 months; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days

Study	Dogan 2003[101]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Germany; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention time: Only immediate postoperative period mentioned
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not reported
Stratum	Mixed/unclear aortic valve disease: Mixture of regurgitation and stenosis in each group
Subgroup analysis within study	Not applicable
Inclusion criteria	Scheduled for elective aortic valve surgery
Exclusion criteria	Patients scheduled for aortic valve replacement with a stentless bioprosthesis or a pulmonary autograft; carotid stenosis >50%; severe calcification of the ascending aorta; history of transient ischaemic attack or stroke; evidence of either Alzheimer's disease or Parkinson's disease
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): Minimally invasive surgery replacement, 65.7 (1.9) years; standard surgery replacement, 64.3 (2.9) years. Gender (M:F): Minimally invasive surgery replacement, 9/11; standard surgery replacement, 11/9. Ethnicity: Not reported

Further population details	1. Age: <75 years (Mean age in both groups <75 years). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not stated / Unclear
Extra comments	Type of valve disease: aortic stenosis, 40 vs 30%; aortic regurgitation, 15 vs. 5%; combination, 45 vs. 65%; mean (SD) systolic gradient, 57 (14) vs. 63 (15) mmHg. Mean (SD) preoperative ejection fraction, 64 (3) vs. 65 (2)%; arterial hypertension, 50 vs 50%; diabetes mellitus, 20 vs. 15%; compensated renal failure, 0 vs. 10%; mean (SD) inspiratory vital capacity, 3.1 (0.9) vs. 3.4 (1.1); mean (SD) forced vital capacity, 3.0 (1.0) vs. 3.2 (1.0); mean (SD) forced expiratory volume in 1 second, 2.3 (0.9) vs. 2.6 (0.8)
Indirectness of population	Serious indirectness: Mixture of stenosis and regurgitation in each group
Interventions	(n=20) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves. Minimally invasive surgery replacement. Induction of anaesthesia standard fashion both groups. Propofol infusion to maintain anaesthesia during postoperative ventilation to promote early extubation. Limited median skin incision (7-9 cm) and a reversed L-shaped upper partial sternotomy into the 4th or 5th right intercostal space, preserving right internal thoracic artery. Cannulation same as in standard surgery group. Type of valve used unclear. Left heart vented via right upper pulmonary vein. Cardioplegia delivered anterograde using aortic root cannula and after aortotomy by selective coronary intubation. Deairing procedures restricted to aortic root. Duration NA - surgical procedure. Concurrent medication/care: All patients received a temporary pacing wire to right ventricle. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear (n=20) Intervention 2: Standard surgery replacement with biological or mechanical valves. Complete sternotomy. Induction of anaesthesia standard fashion both groups. Propofol infusion to maintain anaesthesia during postoperative ventilation to promote early extubation. Following cannulation of ascending aorta and right atrium, vent line introduced via the apex to decompress the left ventricule. Cardioplegic arrest achieved via infusion of anterograde and retrograde cold blood cardioplegia. Following replacement of valve, heart deaired via apex and aortic root. Duration NA - surgical procedure. Concurrent medication/care: All patients received a temporary pacing wire to right ventricle. Indirectness: No indirectness

	Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINIMALLY INVASIVE SURGERY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES versus STANDARD SURGERY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: Cardiac mortality at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: Mortality at Postoperative - unclear follow-up; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Follow-up likely <3 months; Baseline details: Differences in proportion with each type of valve disease, difference for systolic gradient; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Mortality at Postoperative - unclear follow-up; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Differences in proportion with each type of valve disease, difference for systolic gradient; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Stroke at Postoperative - unclear follow-up; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with each type of valve disease, difference for systolic gradient; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Intervention-related major bleeding at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Re-exploration for bleeding at Postoperative - unclear follow-up; Group 1: 1/20, Group 2: 1/20
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with each type of

valve disease, difference for systolic gradient; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Length of hospital stay at after intervention - Actual outcome for Mixed/unclear aortic valve disease: Hospital length of stay at Postoperative - unclear follow-up; Group 1: mean 9.3 Days (SD 1); n=20, Group 2: mean 9.4 Days (SD 1.5); n=20; Comments: Unclear if postoperative stay only Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with each type of valve disease, difference for systolic gradient; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Intervention-related pacemaker implantation at 30 days - Actual outcome for Mixed/unclear aortic valve disease: Permanent pacemaker implantation at Postoperative - unclear follow-up; Group 1: 1/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with each type of valve disease, difference for systolic gradient; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Need for re-intervention at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study	Dogan 2005[100]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Germany; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Up to 2 months follow-up postoperatively
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not mentioned
Stratum	Mitral regurgitation: >75% of study population had mitral regurgitation, but not all
Subgroup analysis within study	Not applicable
Inclusion criteria	Severe mitral valve disease (stenosis, regurgitation or both) scheduled for elective mitral valve operation
Exclusion criteria	Haemodynamically significant coronary disease; internal carotid artery stenosis >70% luminal narrowing; bilateral external iliac or femoral artery stenosis; moderate or severe aortic valve disease; calcified ascending aorta.
Recruitment/selection of patients	Consecutive over a period of 1 year
Age, gender and ethnicity	Age - Mean (SD): Minimally invasive, 60.1 (12.3) years; median sternotomy, 63.2 (13.6) years. Gender (M:F): Minimally invasive, 9/11; median sternotomy, 10/10. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean age in both groups <75 years). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable (Majority mitral regurgitation so included within this stratum). 4.

	Operative risk (for AS and MR): Not stated / Unclear (Not reported). 5. Primary vs secondary valve disease (for MR and TR): Not stated / Unclear (Not reported). 6. Systolic dysfunction (for AR): Not applicable
Extra comments	Mean (SD) preoperative ejection fraction, 63.4 (10.6) vs. 65.2 (11.6)%; mean (SD) preoperative NYHA class, 3.0 (0.3) vs. 2.9 (0.4); valve disease: moderate MS (5 vs. 20%), severe MS (10 vs. 10%), moderate MR (50 vs. 50%), severe MR (35 vs. 20%) and combined mitral valve lesion (15 vs. 15%); mild aortic valve disease, 10 vs. 10%; tricuspid valve disease, 5 vs. 20%; arterial hypertension, 45 vs. 55%; atrial fibrillation, 15 vs. 10%; pulmonary hypertension, 70 vs. 60%; right heart insufficiency, 10 vs. 20%; previous closed mitral commissurotomy, 5 vs. 0%; mean (SD) preoperative vital capacity, 3.6 (1.5) vs. 3.3 (0.99); mean (SD) preoperative forced vital capacity, 3.5 (1.6) vs. 3.2 (1.1); mean (SD) preoperative forced expiratory volume in first second, 2.6 (1.2) vs. 2.5 (0.9)
Indirectness of population	Serious indirectness: Includes proportion with mitral stenosis rather than regurgitation. >75% with mitral regurgitation so included in this stratum.
Interventions	(n=20) Intervention 1: Minimally invasive surgery (mixed repair/replacement) - Port access. Minimally invasive surgery. Limited access through right anterior small (5-7 cm) thoracotomy and peripheral cannulation. Anaesthesia induced with etomidate, sufentanyl and pancuronium and maintained with propofol and sufentanyl. Single lung ventilation used for the minimally invasive procedure. Small right anterior thoracotomy performed through fourth intercostal space. For port access perfusion, the right femoral vessels were cannulated. Transoesophageal guidance was used to perform the procedure. After inverted T pericardiotomy ventral to the right phrenic nerve, a left atriotomy was performed in interatrial groove to expose mitral valve. Mitral valve repair procedures performed according to cited method and replacement procedures were performed with preservation of subvalvular apparatus. Duration N/A - surgical procedure. Concurrent medication/care: A temporary right ventricular pacing wire was placed in all patients in both groups. All patients maintained on Coumarin for the first 3 months following operation. The medication was discontinued in patients with sinus rhythm and patients that underwent reconstruction or bioprosthetic valve replacement. In patients with atrial fibrillation or mechanical valve replacement, oral anticoagulation was maintained. Indirectness: Serious indirectness; Indirectness comment: Mixture of repair and replacement procedures. Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter procedure). 2. Valve type: Not stated / Unclear (Not all patients had replacement in this study - majority

	were repair. For those that had replacement, a mixture of biological and mechanical valves were used). Comments: Two senior surgeons performed all procedures (n=20) Intervention 2: Standard surgery (mixed repair/replacement) - Median sternotomy (mixed repair/replacement). Full median sternotomy. Anaesthesia induced with etomidate, sufentanyl and pancuronium and maintained with propofol and sufentanyl. Following systemic heparinisation they underwent aortobicaval cannulation for standard cardiopulmonary bypass. Left atrium opended at interatrial groove and mitral valve exposed. Mitral valve repair procedures performed according to cited method and replacement procedures were performed with preservation of subvalvular apparatus. Duration N/A - surgical procedure. Concurrent medication/care: A temporary right ventricular pacing wire was placed in all patients in both groups. All patients maintained on Coumarin for the first 3 months following operation. The medication was discontinued in patients with sinus rhythm and patients that underwent reconstruction or bioprosthetic valve replacement. In patients with atrial fibrillation or mechanical valve replacement, oral anticoagulation was maintained. Indirectness: Serious indirectness; Indirectness comment: Mixture of repair and replacement procedures Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter procedure). 2. Valve type: Not stated / Unclear (Not all patients had replacement in this study - majority were repair. For those that had replacement, a mixture of biological and mechanical valves were used). Comments: Two senior surgeons performed all procedures
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PORT ACCESS (RIGHT ANTERIOR SMALL THORACOTOMY) versus MEDIAN STERNOTOMY (MIXED REPAIR/REPLACEMENT) Protocol outcome 1: Cardiac mortality at ≥12 months - Actual outcome for Mitral regurgitation: Hospital mortality at In-hospital; Group 1: 0/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Follow-up <3 months; Baseline details: Some	

differences in terms of proportion with severe and moderate disease.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Mitral regurgitation: Hospital mortality at In-hospital; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences in terms of proportion with severe and moderate disease.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Onset or exacerbation of heart failure at ≥12 months
- Actual outcome for Mitral regurgitation: Left heart decompensation at Postoperative period; Group 1: 1/20, Group 2: 1/20; Comments: Inotropic support was sufficient and no patient required insertion of intraaortic balloon.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Time-point not specified but appears to be immediate postoperative period they are discussing, so <3 months follow-up.; Baseline details: Some differences in terms of proportion with severe and moderate disease.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral regurgitation: Transient ischaemic attack at Postoperative period; Group 1: 1/20, Group 2: 1/20; Comments: 1 TIA in each group. Resolved within 24 h of occurrence.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: Time-point not specified but appears to be immediate postoperative period they are discussing; Baseline details: Some differences in terms of proportion with severe and moderate disease.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Intervention-related major bleeding at 30 days
- Actual outcome for Mitral regurgitation: Rethoracotomy for surgical bleeding at Postoperative period; Group 1: 0/20, Group 2: 1/20
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: Time-point not specified but appears to be immediate postoperative period they are discussing; Baseline details: Some differences in terms of proportion with severe and moderate disease.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Intervention-related pacemaker implantation at 30 days

- Actual outcome for Mitral regurgitation: Permanent pacemaker implantation at Postoperative period; Group 1: 0/20, Group 2: 1/20; Comments: Pacemaker implanted due to sustained ventricular bradycardia Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: Time-point not specified but appears to be immediate postoperative period they are discussing; Baseline details: Some differences in terms of proportion with severe and moderate disease.; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Quality of life at ≥12 months; Need for re-intervention at ≥12 months; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study	TRICAVAL trial: Dreger 2020[106]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in Germany; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Follow-up to 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TR grading by echocardiography
Stratum	Tricuspid regurgitation: Severe symptomatic tricupid regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	NYHA class ≥II despite established optimal medical therapy; age ≥50 years; and high surgical risk (logistic EuroSCORE I ≥15% or other contraindications for conventional valve surgery according to the decision of the local heart team)
Exclusion criteria	Severe left ventricular dysfunction with LVEF <30%; severe kidney dysfunction; IVC diameter at site of implantation >32 mm; severe mitral regurgitation;estimated life expectancy <12 months due to carcinoma, chronic liver disease, chronic renal disease or chronic end-stage pulmonary disease; acute myocardial infarction ≤1 month prior to treatment; stroke/transient ischaemic attack in last 180 days; leukopenia (white blood cell count <3,000 cell/ml); anaemia (haemoglobin <9 g/dl); thrombocytopaenia (platelet count <50,000 cells/ml) or any known blood clotting disorder; evidence of intracardiac mass, thrombus or vegetation in the right heart; active upper GI bleeding within 1 month of procedure; patients with an acute emergency; contraindication of hypersensitivity to all anticoagulation regimens or inability to be anticoagulated for procedure; allergy against use of implanted stent/prosthesis; undergoing regular dialysis

	or a serum creatinine >3.0 ml/dl; unsuitable for implantation due to thrombosis of lower venous system or vena cava filter; active bacterial endocarditis within 6 months prior to procedure; women of childbearing potential without highlight effective contraception (PEARL Index <1%); inability to comply with all study procedure and follow-up visits; and subjects detained legally in an official institute.
Recruitment/selection of patients	Unclear if consecutive
Age, gender and ethnicity	Age - Median (IQR): CAVI, 77 (68.2-82.0) years; medical, 77 (72.2-79.5) years. Gender (M:F): CAVI, 2/12; medical, 7/7. Ethnicity: Not reported.
Further population details	1. Age: 75 years or over (Median age >75 years in both groups, though interquartile range dips below 75 years). 2. Childbearing age: Women not of childbearing age (≥45 years) (Only includes those 50 years or over). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not applicable 5. Primary vs secondary valve disease (for MR and TR): Not stated / Unclear (Unclear though likely to be secondary as all had heart failure as well). 6. Systolic dysfunction (for AR): Not applicable
Extra comments	Study was prematurely terminated due to fourth device-related complication (dislocation of valve). Four patients had severe TR, four had massive TR and twenty had torrential TR. NYHA class II (14% vs. 21%), III (86% vs. 71%) and IV (0% vs. 7%); mean (SD) logistic EuroSCORE, 14.6 (11.6)% vs. 14.2 (7.9)%; mean (SD) BMI, 25.5 (4.6) vs. 25.0 (4.1) kg/m^2; mean (SD) LVEF, 56.4 (6.4)% vs. 58.1 (7.1)%; mean (SD) effective regurgitant orifice area, 1.23 (0.6) vs. 1.35 (1.1) cm^2; mean (SD) regurgitant volume, 68.7 (24.6) vs. 74.4 (17.3) ml; mean (SD) TAPSE, 16.1 (5.2) vs. 14.8 (5.1) mm; mean (SD) RV diameter, 49.0 (6.6) vs. 54.6 (7.4) mm; mean (SD) RV area, 33.5 (15.3) vs. 35.8 (9.7) cm^2; median (IQR) systolic pulmonary artery pressure, 39.0 (33.5-55.5) vs. 40.0 (32.8-46.8) mmHg; mean (SD) NT-proBNP, 2,243 (979) vs. 3,294 (2,447) ng/l; mean (SD) creatinine, 1.5 (0.5) vs. 1.4 (0.4) mg/dl; mean (SD) MLHFQ score, 41.9 (15.1) vs. 41.8 (14.0); mean (SD) 6 min walk test, 294 (115) vs. 286 (114) m; history of heart surgery, 21% vs. 43%; HF with preserved EF, 86% vs. 93%; HF with mid-range ejection fraction (40-49%), 14% vs. 7%; diuretics, 100% vs. 100%; beta-blockers, 86% vs. 79%; ACE inhibitors, 79% vs. 43%; mineralocorticoid receptor antagonist, 71% vs. 64%.
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Transcatheter repair. Implantations were performed via right transfemoral venous access under local anaesthesia and guided by transthoracic echocardiography. Unfractionated heparin

	given to reach activating clotting time >250 seconds. Landing zone prepared by implantation of self-expanding nitinol stent into IVC protruding 5-10 mm into right atrium depending on IVC anatomy. 23, 26 or 29 mm Edwards SAPIEN XT transcatheter valve then implanted into junction of IVC and right atrium. After sheath was removed, haemostasis achieved by Z-suture of skin and manual compression. All patients received oral anticoagulation following implantation. Duration Intervention (+ up to 12 months medical?). Concurrent medication/care: Unclear, but appears that optimal medical treatment also continued in this group. Optimal medical therapy was determined by heart failure specialists and defined as medical therapy as recommended by current heart failure guidelines. For patents with preserved ejection fraction, this was defined as the maximum tolerable dose of diuretics controlling oedema. At baseline, 100% received diuretics, 86% received beta-blockers, 79% received ACE inhibitors and 71% received a mineralocorticoid receptor antagonist. . Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Transfemoral 2. Valve type: Not applicable (n=14) Intervention 2: Conservative management - Pharmacological management. Optimal medical treatment continued. Optimal medical therapy was determined by heart failure specialists and defined as medical therapy as recommended by current heart failure guidelines. For patents with preserved ejection fraction, this was defined as the maximum tolerable dose of diuretics controlling oedema. At baseline, 100% received diuretics, 79% received beta-blockers, 43% received ACE inhibitors and 64% received a mineralocorticoid receptor antagonist. Duration Up to 12 months medical?. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not applicable
Funding	Study funded by industry (Study financially supported by Edwards Lifesciences. Authors received funding from academic/other sources: Berlin Institute of Health, Universitätsmedizin Berlin and Deutsche Herzstiftung.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR (CAVI) versus PHARMACOLOGICAL MANAGEMENT (OPTIMAL MEDICAL TREATMENT)

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Tricuspid regurgitation: All-cause mortality at 12 months; Group 1: 8/14, Group 2: 4/14; Comments: Deaths were due to: right heart failure (n=4 in CAVI and n=3 in medical), sepsis (n=3 in CAVI and n=1 in medical) or haemorrhage (n=1 in CAVI).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Though randomised, differences remain between groups due to small study sample: NYHA class, regurgitant volume, history of heart surgery and NT-proBNP; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Tricuspid regurgitation: Mortality due to right heart failure at 12 months; Group 1: 4/14, Group 2: 3/14; Comments: All were due to right heart failure. Other deaths within 12 month period do not appear to be cardiac-related (sepsis or haemorrhage).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Though randomised, differences remain between groups due to small study sample: NYHA class, regurgitant volume, history of heart surgery and NT-proBNP; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Interevention-related mortality at 30 days
- Actual outcome for Tricuspid regurgitation: In-hospital mortality at In-hospital; Group 1: 3/14, Group 2: 0/14; Comments: The three in-hospital deaths in the CAVI group were due to haemorrhagic shock due to resuscitation-related splenic rupture following conversion to surgery (n=1), acute-on-chronic right heart failure (n=1) and pneumonia (n=1).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Though randomised, differences remain between groups due to small study sample: NYHA class, regurgitant volume, history of heart surgery and NT-proBNP; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Tricuspid regurgitation: Change in Minnesota Living with Heart Failure Questionnaire score compared to baseline at 3 months; Group 1: mean -19.9 (SD 13.1); n=8, Group 2: mean -7.6 (SD 16.3); n=11; Comments: Higher scores on this questionnaire indicate worse impairment, so

a larger reduction compared to baseline indications more improvement in that group
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Though randomised, differences remain between groups due to small study sample: NYHA class, regurgitant volume, history of heart surgery and NT-proBNP; Group 1 Number missing: 6, Reason: n=4 in-hospital deaths, n=2 unclear; Group 2 Number missing: 3, Reason: Unclear

Protocol outcome 5: Onset or exacerbation of heart failure at ≥12 months
- Actual outcome for Tricuspid regurgitation: NYHA class worsening by 1 or 2 classes compared to baseline at 3 months; Group 1: 0/8, Group 2: 1/11; Comments: n=1 in medical group worsened by 2 classes compared to baseline
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Though randomised, differences remain between groups due to small study sample: NYHA class, regurgitant volume, history of heart surgery and NT-proBNP; Group 1 Number missing: 6, Reason: n=4 in-hospital deaths, n=2 unclear; Group 2 Number missing: 3, Reason: Unclear

Protocol outcome 6: Intervention-related major bleeding at 30 days
- Actual outcome for Tricuspid regurgitation: Haemorrhage at 30 days; Group 1: 1/14, Group 2: 0/14; Comments: Only one bleeding event mentioned (haemorrhage), occurring in the CAVI group and leading to in-hospital death. Caused by reuscitation-related splenic rupture following conversion to surgery.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Though randomised, differences remain between groups due to small study sample: NYHA class, regurgitant volume, history of heart surgery and NT-proBNP; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Need for re-intervention at ≥12 months
- Actual outcome for Tricuspid regurgitation: Need for open heart surgery at 48 h post-implantation; Group 1: 4/14, Group 2: 0/14; Comments: All four were due to delayed major complications of the valve implantation, occurring 7-48 h after primarily successful implantations and resulted in open heart surgery (n=2 cardiac tamponades due to stent migration and n=2 valve dislocations). These complications led to patient recruitment being stopped due to safety concerns.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: All events occurred within 48 h of procedure and unclear if any further reinterventions required during longer follow-up; Baseline details: Though randomised, differences remain between groups due to small study sample: NYHA class, regurgitant volume, history of heart surgery and NT-proBNP; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 8: Re-hospitalisation at ≥12 months - Actual outcome for Tricuspid regurgitation: Hospitalisation for heart failure at 12 months; Group 1: 4/14, Group 2: 4/14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Though randomised, differences remain between groups due to small study sample: NYHA class, regurgitant volume, history of heart surgery and NT-proBNP; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 9: Major vascular complications at 30 days - Actual outcome for Tricuspid regurgitation: Major vascular complications at 30 days; Group 1: 0/14, Group 2: 0/14; Comments: Said to be no major vascular complications in the study (valve dislocations and stent migrations captured under need for reintervention). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Though randomised, differences remain between groups due to small study sample: NYHA class, regurgitant volume, history of heart surgery and NT-proBNP; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Intervention-related stroke or TIA at 30 days; Length of hospital stay at after intervention; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Renal failure at 30 days

Study	El Ashkar 2016[110]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=34)
Countries and setting	Conducted in Egypt; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention time: Intervention and immediate postoperative outcomes only
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Mixed/unclear mitral valve disease: Described as those with isolated rheumatic mitral valve disease requiring replacement - no indication as to how many with stenosis/regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Isolated rheumatic mitral valve disease requiring mitral valve replacement
Exclusion criteria	Patients with left atrial thrombus; other valve pathologies; ischemic heart disease; redo cases; significant comorbidities; morbid obesity
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Minimally invasive, 43.4 (11.41) years; median sternotomy, 41.6 (11.94) years. Gender (M:F): Minimally invasive, 12/5; median sternotomy, 13/4. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean age in both groups <75 years). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not stated / Unclear (Proportion with MS unclear as well as morphology for these

	patients). 4. Operative risk (for AS and MR): Not stated / Unclear (Proportion with MR unclear as well as operative risk for these patients). 5. Primary vs secondary valve disease (for MR and TR): Not stated / Unclear (Proportion with MR unclear as well as whether disease was primary/secondary for these patients). 6. Systolic dysfunction (for AR): Not applicable
Extra comments	Mean (SD) ejection fraction, 63.2 (4.7) vs. 62.54 (8.2)%; mean (SD) pulmonary artery systolic pressure, 48.0 (6.3) vs. 45.0 (13.8) mmHg
Indirectness of population	Serious indirectness: Mixed/unclear type of mitral valve disease
Interventions	(n=17) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Minimally invasive surgery replacement with mechanical valve. Mitral valve replacement performed via small anterolateral, video-assisted minithoracotomy. The right thoracotomy was carried out just lateral to the nipple in males and in the mammary crease in females and over the right 4th intercostal space for 7-8 cm. Cardiopulmonary bypass was the initiated, the lung deflated to expose the pericardium which was opened just ventral to the phrenic nerve, up to expose the ascending aorta and down to the diaphragm. A 30° camera was used for video-assisted visualization and placed through a separate incision just anterior to the one used for the aortic clamp. Left atrium was opened and valve replacement was performed with preservation of posterior leaflet. Mechanical valves used in all cases. Duration N/A - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter procedure). 2. Valve type: Mechanical (Mechanical valves used in all cases). (n=17) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with mechanical valve. Mitral valve replacement performed through median sternotomy. No further details. Type of valve not mentioned for this group but possible all mechanical as with other minimally invasive group?. Duration N/A - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter procedure). 2. Valve type: Mechanical (Not explicitly stated for this group but all mechanical in the other group - may apply to this group as well but the wording is unclear?).

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINIMALLY INVASIVE SURGERY REPLACEMENT WITH MECHANICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH MECHANICAL VALVE Protocol outcome 1: Cardiac mortality at ≥12 months - Actual outcome for Mixed/unclear mitral valve disease: Mortality at In-hospital; Group 1: 0/17, Group 2: 0/17 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: <3 months follow-up; Baseline details: Only gives details for small number of factors; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Intervention-related mortality at 30 days - Actual outcome for Mixed/unclear mitral valve disease: Mortality at In-hospital; Group 1: 0/17, Group 2: 0/17 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Only gives details for small number of factors; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Length of hospital stay at after intervention - Actual outcome for Mixed/unclear mitral valve disease: Intensive care unit stay at In-hospital; Group 1: mean 3 (SD 1.78); n=17, Group 2: mean 3.72 (SD 1.9); n=17 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Intensive care unit stay is different to overall hospital stay; Baseline details: Only gives details for small number of factors; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Intervention-related major bleeding at 30 days; Need for re-intervention at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study	El-Fiky 2000[109]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Egypt; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention time: Appears to be intervention and immediate postoperative period only
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Mixed/unclear mitral valve disease: Mitral valve patients -majority had both stenosis and regurgitation. Unclear which driving intervention need.
Subgroup analysis within study	Not applicable
Inclusion criteria	Mitral valve disease
Exclusion criteria	Previous cardiac surgery; associated coronary artery disease; associated aortic valve disease requiring intervention; failure to give informed consent
Recruitment/selection of patients	Consecutive patients willing to participate
Age, gender and ethnicity	Age - Mean (SD): Minimally invasive: 22 (10) years; median sternotomy, 23 (9) years. Gender (M:F): Minimally invasive: 5/45; median sternotomy, 7/43. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean age <75 years in both groups). 2. Childbearing age: Women of childbearing age (<45) (Majority in study are women and mean age <45 years in both groups). 3. Morphology (for MS): Not

	stated / Unclear (Proportion with MS unclear as well as morphology for those with MS). 4. Operative risk (for AS and MR): Not stated / Unclear (Proportion with MR unclear as well as operative risk for those with MR). 5. Primary vs secondary valve disease (for MR and TR): Not stated / Unclear (Proportion with MR unclear as well as primary/secondary disease for those with MR). 6. Systolic dysfunction (for AR): Not applicable
Extra comments	Disease type: rheumatic (92 vs. 96%) and congenital (8 vs. 4%); mean (SD) NYHA class, 2.7 (0.6) vs. 2.9 (0.8); mean (SD) LVEF, 45 (8) vs. 48 (9)%; procedure: replacement (92 vs. 94%) and repair (8 vs. 6%)
Indirectness of population	Serious indirectness: Mixed mitral valve disease population - majority had both stenosis and regurgitation. Unclear which driving intervention need. Also some with congenital disease but <10%
Interventions	(n=50) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Port access replacement with biological or mechanical valve. A 10-12 cm incision was created in right submammary fold starting 3-5 cm from lateral border of sternum. Right chest cavity entered through fourth intercostal space. Pericardial sac entered through an incision 2-3 cm anterior and parallel to phrenic nerve extending from diaphragm to the aortic reflection. Aortic and bicaval cannulation performed and cardiopulmonary bypass instituted. Left atrium opened through incision posterior and parallel to interatrial groove giving access to mitral valve. Repair or replacement was then performed. Duration N/A - surgical procedure. Concurrent medication/care: Not reported. Indirectness: Serious indirectness; Indirectness comment: Minority (8%) had valve repair rather than replacement procedures Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter procedure). 2. Valve type: Not stated / Unclear (Not all patients underwent replacement and the type of valve used for those that underwent replacement is not stated). (n=50) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Operative technique was essentially the same as in the port access group but the approach was through median sternotomy. Duration N/A - surgical procedure. Concurrent medication/care: Not reported. Indirectness: Serious indirectness; Indirectness comment: Minority (6%) had valve repair rather than replacement procedures Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not a transcatheter procedure). 2. Valve type: Not stated / Unclear (Not all patients underwent replacement and the type of valve used for those that underwent replacement is not stated).

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PORT ACCESS REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES Protocol outcome 1: Cardiac mortality at ≥12 months - Actual outcome for Mixed/unclear mitral valve disease: In-hospital mortality at In-hospital; Group 1: 0/50, Group 2: 0/50 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: In-hospital data rather than longer term outcome; Baseline details: Details given for only a limited number of factors; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Intervention-related mortality at 30 days - Actual outcome for Mixed/unclear mitral valve disease: In-hospital mortality at In-hospital; Group 1: 0/50, Group 2: 0/50 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Details given for only a limited number of factors; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Length of hospital stay at after intervention - Actual outcome for Mixed/unclear mitral valve disease: Length of stay at In-hospital; Group 1: mean 7 days (SD 2); n=50, Group 2: mean 7 days (SD 2); n=50 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Details given for only a limited number of factors; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Intervention-related major bleeding at 30 days; Need for re-intervention at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study	Fareed 2018[119]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Egypt; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Mixed/unclear aortic valve disease
Subgroup analysis within study	Not applicable:
Inclusion criteria	People with aortic valve disease (type not specified) requiring aortic valve replacement
Exclusion criteria	People undergoing concomitant valve surgery rather than aortic valve surgery, coronary artery bypass grafting or reoperation, people with endocarditis
Age, gender and ethnicity	Age - Other: Not stated. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Age: Not stated / Unclear 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not stated / Unclear
Indirectness of population	--

Interventions	(n=30) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves. Limited upper mini-sternotomy to the 3rd right intercostal space. Duration N/A - surgical procedure. Concurrent medication/care: Conventional anaesthetic technique used (same as control group). Otherwise not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear (n=30) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Traditional sternotomy. Duration N/A - surgical procedure. Concurrent medication/care: Conventional anaesthetic technique used (same as control group). Otherwise not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINIMALLY INVASIVE SURGERY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: Length of hospital stay at after intervention
- Actual outcome for Mixed/unclear aortic valve disease: Total hospital stay at After intervention; Group 1: mean 7 days (SD 0.8); n=30, Group 2: mean 8.8 days (SD 0.8); n=30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Reports that that was no statistically significant difference with a P value more than 0.05 as regards the age, sex, NYHA class, preoperative echocadiographic findings and also preoperative spirometric studies. But not values given.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Postoperative arrhythmias at <3 months; Group 1: 6/30, Group 2: 11/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Does not specific the type of arrhythmias. Therefore, may

include other arrhythmias.; Baseline details: Reports that that was no statistically significant difference with a P value more than 0.05 as regards the age, sex, NYHA class, preoperative echocadiographic findings and also preoperative spirometric studies. But not values given.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Intervention-related mortality at 30 days; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Intervention-related major bleeding at 30 days; Need for re-intervention at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study (subsidiary papers)	**Feldman 2011[120] (Feldman 2015[121], Glower 2012[137], Gucuk ipek 2018[149], Herrmann 2012[159], Lim 2014[217], Mauri 2013[242], Mauri 2010[243])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=279)
Countries and setting	Conducted in Canada, USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography as per inclusion criteria
Stratum	Mitral regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Moderate-severe or severe chronic mitral regurgitation and symptomatic with >25% LVEF and LVESD ≤55mm or asymptomatic with one or more of the following: LVEF 25-60%, LVESD ≥40mm, new onset of AF, pulmonary hypertension defined as pulmonary artery systolic pressure >50mmHg at rest or >60mmHg with exercise, candidate for MV repair or replacement surgery, including cardiopulmonary bypass, the primary regurgitant jet originates from malcoaptation of the A2 and P2 scallops of the mitral valve. If a secondary jet exists, it must be considered clinically insignificant.
Exclusion criteria	Acute myocardial infarction in the prior 12 weeks of intended treatment, the need for any other cardiac surgery, any endovascular therapeutic interventional or surgical procedure performed within 30 days prior, ejection fraction <25% and/or end-systolic dimension >55mm, mitral valve orifice area <4.0cm², if leaflet flail is present: width of flail segment ≥15mm or flail gap ≥10mm, if leaflet tethering is present: coaption depth >11mm or vertical coaptation length is <2mm, severe mitral annular calcification, leaflet anatomy that may

	preclude clip implantation, preoper clip positioning on the leaflets, or sufficient reduction in mitral regurgitation (this may include the following: evidence of calcification in the grasping area of the A2 and/or P2 scallops, presence of a significant cleft of A2 or P2 scallops, more than 1 anatomic criteria dimensionally near the exclusion limits, bileaflet flail or severe bileaflet prolapse, lack of both primary and secondary chordal support), prior MV surgery or valvuloplasty or any currently implanted mechanical prosthetic valve or currently implanted ventricular assist device, echocardiographic evidence of intracardiac mass, thrombus or vegetation, history of or active endocarditis or rheumatic heart disease, history of atrial septal defect or patent foramen ovale associated with clinical symptoms
Recruitment/selection of patients	Recruited from 37 study centers in the United States and Canada
Age, gender and ethnicity	Age - Other: Mean intervention: 67.3±12.8, mean control: 65.7±12.9. Gender (M:F): 178:101. Ethnicity: Not stated
Further population details	1. Age: Mixed (Mean intervention: 67.3±12.8, mean control: 65.7±12.9). 2. Childbearing age: Women not of childbearing age (≥45 years) (Based on mean age). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear 5. Primary vs secondary valve disease (for MR and TR): Not stated / Unclear 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=184) Intervention 1: Transcatheter repair. MitraClip. Catheter-based device through clip. Performed via the femoral vein with echo and fluoroscopic guidance under general anaesthetic. Heparin given during the procedure. Duration N/A - surgical procedure. Concurrent medication/care: After the procedure people receive aspirin 325mg once a day for 6 months and clopidogrel for 30 days. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Not applicable (n=95) Intervention 2: Surgical repair (unclear/mixed invasiveness). Mitral valve repair in 86% of people and mitral valve replacement in 14% of people. Duration N/A - surgical procedure. Concurrent medication/care: Not stated. Indirectness: Serious indirectness; Indirectness comment: Mixed valve repair and replacement and unclear invasiveness of surgery

	Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear Comments: mixture of repair and replacement and unclear invasiveness of surgery
Funding	Study funded by industry (Abbott Vascular)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus SURGICAL REPAIR/REPLACEMENT (UNCLEAR/MIXED INVASIVENESS)

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral regurgitation: Death at 5 years; Group 1: 32/154, Group 2: 15/56
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30, Reason: 6 not treated as withdrew consent. Further 24 excluded due to: missing 5-year visit (n=3), missing or unevaluable MR grade at 5 year visit (n=5), withdrawal of consent (n=16); Group 2 Number missing: 39, Reason: 15 not treated as withdrew consent. Further 24 excluded due to: missing 5-year visit (n=2), missing or unevaluable MR grade at 5 year visit (n=7), withdrawal of consent (n=15)

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Mitral regurgitation: Death at 30 days; Group 1: 2/180, Group 2: 2/94
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 4 withdrawn or lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up

Protocol outcome 3: Quality of life at ≥12 months
- Actual outcome for Mitral regurgitation: SF-36 physical component summary at 1 year; Group 1: mean 4.4 (SD 9.8); n=132, Group 2: mean 4.4 (SD 10.4); n=60; SF-36 physical component summary 0-100 Top=High is good outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 52, Reason: States number with reading at 1 year was 132. Reason data missing unclear for all participants.; Group 2 Number missing: 35, Reason: States number with reading at 1 year was 60. Reason data missing unclear for all participants.
- Actual outcome for Mitral regurgitation: SF-36 mental component summary at 1 year; Group 1: mean 5.7 (SD 9.9); n=133, Group 2: mean 3.8 (SD 10.3);

n=60; SF-36 Mental component summary 0-100 Top=High is good outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 51, Reason: States number with reading at 1 year was 133. Reason data missing unclear for all participants.; Group 2 Number missing: 35, Reason: States number with reading at 1 year was 60. Reason data missing unclear for all participants.

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral regurgitation: Major stroke at 30 days; Group 1: 2/180, Group 2: 2/94
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Does not include TIA; Group 1 Number missing: 4, Reason: 4 withdrawn or lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up

Protocol outcome 5: Intervention-related major bleeding at 30 days
- Actual outcome for Mitral regurgitation: Transfusion of ≥2 units of blood at 30 days; Group 1: 24/180, Group 2: 42/94
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear if directly related to bleeding; Group 1 Number missing: 4, Reason: 4 withdrawn or lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up

Protocol outcome 6: Need for re-intervention at ≥12 months
- Actual outcome for Mitral regurgitation: MV surgery or reoperation at 5 years; Group 1: 43/154, Group 2: 5/56
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30, Reason: 6 not treated and withdrew consent. Further 24 excluded due to: missing 5-year visit (n=3), missing or unevaluable MR grade at 5 year visit (n=5), withdrawal of consent (n=16); Group 2 Number missing: 39, Reason: 15 not treated band withdrew consent. Further 24 excluded due to: missing 5-year visit (n=2), missing or unevaluable MR grade at 5 year visit (n=7), withdrawal of consent (n=15)

Protocol outcome 7: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Mitral regurgitation: New onset of permanent atrial fibrillation at 30 days; Group 1: 2/180, Group 2: 0/94
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 4 withdrawn or lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up

Protocol outcome 8: Major vascular complications at 30 days - Actual outcome for Mitral regurgitation: Urgent or emergency cardiovascular surgery for adverse events at 30 days; Group 1: 4/180, Group 2: 4/94 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not necessarily due to vascular complications; Group 1 Number missing: 4, Reason: 4 withdrawn or lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up Protocol outcome 9: Renal failure at 30 days - Actual outcome for Mitral regurgitation: Renal failure at 30 days; Group 1: 1/180, Group 2: 0/94 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 4 withdrawn or lost to follow up; Group 2 Number missing: 1, Reason: 1 lost to follow up	
Protocol outcomes not reported by the study	Cardiac mortality at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Prosthetic valve endocarditis at ≥12 months

Study (subsidiary papers)	**Leon 2010[213] (Douglas 2015[103], Kapadia 2015[183], Kapadia 2014[184], Makkar 2012[233], Passeri 2015[287], Reynolds 2011[316], Reynolds 2012[318], Svensson 2014[371], Kapadia 2015[181])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=358)
Countries and setting	Conducted in Canada, Germany, USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography defined criteria
Stratum	Aortic stenosis (non-bicuspid):
Subgroup analysis within study	Not applicable:
Inclusion criteria	People with severe aortic stenosis (AVA <0.8cm^2, mean AV gradient ≥40mmHg, or a peak aortic jet velocity of ≥4m/s) and cardiac symptoms (all included were NYHA class II-IV) for whom conventional surgery to replace the aortic valve was associated with high risk (coexisting conditions that are associated with a predicted risk of death by 30 days after surgery of ≥50%).
Exclusion criteria	Bicuspid or noncalcified aortic valve, acute MI, substantial coronary artery disease requiring revascularisation, a LVEF <20%, an aortic annulus diameter of <18mm or >25mm, severe (>3+) mitral or aortic regurgitation, a TIA or stroke within the previous 6 months, and severe renal insufficiency, blood dyscrasias, pre-existing prosthetic valve in any position, hypertrophic cardiomyopathy with or without obstruction, need for emergency surgery for any reason, active peptic ulcer or upper GI bleeding within the prior 3 months, echocardiographic evidence of an intracardiac mass, thrombus or vegetation, hypersensitivity to aspirin, heparin, ticlopidine or clopidogrel, or sensitivity to contrast media, significant

	abdominal or thoracic aorta disease, iliofemoral vessel characteristics that would preclude safe placement of a 22F or 24F introducer sheath, currently participating in an investigational drug or another device study, active bacterial endocarditis or other active infections, bulky calcified aortic valve leaflets in close proximity to coronary ostia.
Recruitment/selection of patients	Screened by investigators and then selected by the executive committee (including representatives from Edwards Lifesciences).
Age, gender and ethnicity	Age - Mean (SD): TAVI: 83.1±8.6, standard therapy: 83.2±8.3. Gender (M:F): 166:182. Ethnicity: Not stated
Further population details	1. Age: Mixed (TAVI: 83.1±8.6, standard therapy: 83.2±8.3 - Some patients below 75 on the confidence intervals, but mostly over the age of 75.). 2. Childbearing age: Women not of childbearing age (≥45 years) 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Inoperable (STS score TAVI: 11.2±5.8, STS score standard therapy: 12.1±6.1, logistic EuroSCORE TAVI: 26.4±17.2, logistic EuroSCORE standard therapy: 30.4±19.1). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	Serious indirectness: >10% of people had previous surgical intervention (balloon aortic valvuloplasty)
Interventions	(n=179) Intervention 1: Transcatheter replacement with biological valves. Using Edwards SAPIEN heart valve system (tileaflet bovine pericardial valve and a balloon-expandable, stainless steel support frame). Duration N/A - Surgical intervention. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Transfemoral 2. Valve type: Biological (n=179) Intervention 2: Conservative management - Pharmacological management. Standard therapy - including pharmacological management and balloon aortic valvuloplasty (140 patients had this by 2 years). Duration 2 years. Concurrent medication/care: Not stated. Indirectness: Serious indirectness; Indirectness comment: While this is conservative management, it also includes valve repair in the majority of patients. Further details: 1. Route of transcatheter intervention (in TAVI for AS): Transfemoral 2. Valve type: Not applicable
Funding	Study funded by industry (Edwards Lifesciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPLACEMENT WITH BIOLOGICAL VALVES versus PHARMACOLOGICAL MANAGEMENT

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): All-cause mortality at 5 years; Group 1: Observed events 127 n=179 ; Group 2: Observed events 149 n=179; HR 0.5; Lower CI 0.39 to Upper CI 0.65; Log rank variance: <0.0001; Actuarial or Kaplan Meier curves reported? Kaplan-Meier
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Aortic stenosis (non-bicuspid): All-cause mortality at 5 years; Group 1: 127/176, Group 2: 143/149
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 3, Reason: Reason missing unclear, likely to have withdrawn; Group 2 Number missing: 30, Reason: 20 crossed over and 10 withdrew.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Cardiovascular death at 5 years; Group 1: Observed events 84 n=179 ; Group 2: Observed events 118 n=179; HR 0.41; Lower CI 0.31 to Upper CI 0.55; Log rank variance: <0.0001
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Aortic stenosis (non-bicuspid): Cardiovascular death at 5 years; Group 1: 84/176, Group 2: 118/149
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 3, Reason: Reason missing unclear, likely to have withdrawn; Group 2 Number missing: 30, Reason: 20 crossed over and 10 withdrew.

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 30 days; Group 1: 9/179, Group 2: 5/179

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 1 person withdrew. 5 people died.; Group 2 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 12 people died.

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Stroke or TIA at 30 days; Group 1: 12/179, Group 2: 3/179
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 1 person withdrew. 5 people died.; Group 2 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 12 people died.

Protocol outcome 5: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major bleeding at 30 days; Group 1: 30/179, Group 2: 7/179
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 1 person withdrew. 5 people died.; Group 2 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 12 people died.

Protocol outcome 6: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Cardiac reintervention at 1 year; Group 1: 5/179, Group 2: 87/179; Comments: TAVI: 1 underwent balloon aortic valvuloplasty followed by aortic valve replacement, 3 underwent a repeat TAVI procedure and 1 underwent aortic valve replacement. Standard therapy: 30 had repeat balloon aortic valvuloplasty after index valvuloplasty, 36 had first balloon aortic valvuloplasty more than 30 days after randomisation, 17 underwent aortic valve replacement and 4 underwent TAVI at non-participating sites outside of the USA.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Re-hospitalisation at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Rehospitalisation at 5 years; Group 1: n=179 ; Group 2: n=179; HR 0.4; Lower CI 0.29 to Upper CI 0.55
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Aortic stenosis (non-bicuspid): Rehospitalisation at 2 years; Group 1: 53/179, Group 2: 95/179; Comments: Missing data but unclear which may have had events before death for example.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 8: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New pacemaker at 30 days; Group 1: 6/179, Group 2: 9/179
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 1 person withdrew. 5 people died.; Group 2 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 12 people died.

Protocol outcome 9: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New atrial fibrillation at 30 days; Group 1: 1/179, Group 2: 2/179
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 1 person withdrew. 5 people died.; Group 2 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 12 people died.

Protocol outcome 10: Prosthetic valve endocarditis at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Endocarditis at 2 years; Group 1: 3/179, Group 2: 1/179; Comments: Kaplan-Meier estimates

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0, Reason: Uses Kaplan-Meier estimates. 77 died. Follow up was achieved in 99 out of 102 patients (97.1%) at 2 years.; Group 2 Number missing: 0, Reason: Uses Kaplan-Meier estimates. 5 patients withdrew and 118 died. Patients were allowed to cross over between years 1 and 2 of the study (of which 11 chose to join the TAVR group) Protocol outcome 11: Major vascular complications at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): Major vascular complications at 30 days; Group 1: 29/179, Group 2: 2/179 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 1 person withdrew. 5 people died.; Group 2 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 12 people died. Protocol outcome 12: Renal failure at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): Renal replacement therapy at 30 days; Group 1: 2/179, Group 2: 3/179 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Significantly more patients had atrial fibrillation before treatment in the standard therapy group. Generally the surgical risk score appears to be higher in the standard therapy group.; Group 1 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 1 person withdrew. 5 people died.; Group 2 Number missing: 0, Reason: Reported as 179 people (Kaplan-Meier estimates). 12 people died.	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Length of hospital stay at after intervention

Study (subsidiary papers)	**Leon 2016[214] (Baron 2017[41], Baron 2018[43], Baron 2019[45], Chen 2018[81], Cremer 2018[86], Malaisrie 2018[235], Goodall 2019[142], Greason 2020[145], Makkar 2020[234])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2032)
Countries and setting	Conducted in Canada, USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Specific echocardiographic parameters
Stratum	Aortic stenosis (non-bicuspid)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s and an initial aortic valve area (AVA) of ≤0.8cm² or indexed EOA <0.5cm²/m². Qualifiying echo was within 60 days of the date of the procedure. Patient was symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA functional class II or greater, the heart team agreed that valve implantation would likely benefit the patient, adequate informed consent, the patient agreed to comply to all required post-procedure follow-up visits including annual visits through 5 years. STS ≥4 or <4 if the heart team determines intermediate-risk patient profile with important comorbidities not represented in the STS risk score algorithm, heart team agree on eligibility including assessment that TAVR or AVR is appropriate, heart team agreed on treatment strategy for concomitant coronary disease, study patient agreed to undergo surgical aortic valve replacement if randomised to control treatment.

Exclusion criteria	Heart team assessment of inoperability. Evidence of an acute MI <1 month (30 days) before the intended treatment, aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified, mixed aortic valve disease, preexisting mechanical or bioprosthetic valve in any position, complex coronary artery disease, any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (implantation of a permanent pacemaker is not excluded), any patient with a balloon valvuloplasty within 30 das of the procedure, patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation, blood dyscrasia, hypertrophic cardiomyopathy with or without obstruction, severe ventricular dysfunction with LVEF <20%, echocardiographic evidence of intracardiac mass, thrombus or vegetation, active upper GI bleeding within 3 months, a known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure, native aortic annulus size <18mm or >27mm as measured by echocardiogram, clinically or neuroimaging confirmed stroke or TIA within 6 months of the procedure, renal insufficiency and/or renal replacement therapy at the time of screening, estimated life expectancy <24 months due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease, expectation that patient will not improve despite treatment of aortic stenosis, currently participating in an investigational drug or another device study (note: trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials), active bacterial endocarditis within 6 months of procedure, patient refuses aortic valve replacement surgery
Recruitment/selection of patients	Nothing additional stated
Age, gender and ethnicity	Age - Mean (SD): TAVR: 81.5±6.7, SAVR: 81.7±6.7. Gender (M:F): 1108:924. Ethnicity: Not stated
Further population details	1. Age: 75 years or over (Age range and confidence intervals mostly fall into this category). 2. Childbearing age: Women not of childbearing age (≥45 years) 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Intermediate (As stated in article. STS risk score TAVR: 5.8±2.1, STS risk score SAVR: 5.8±1.9). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness

Interventions	(n=1011) Intervention 1: Transcatheter replacement with biological valves. SAPIEN XT heart valve. Duration N/A - Surgical procedure. Concurrent medication/care: All patients received aspirin (91mg) and clopidogrel (≥300mg) after the procedure and heparin during the procedure. Patients continued to take aspirin indefinitely and clopidogrel for a minimum of 1 month. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Transfemoral (Majority transfemoral (76.3%). The rest transthoracic (23.7%) - with 174 patients having transapical, and 62 having transaortic access). 2. Valve type: Biological (n=1021) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological valve. Standard surgical replacement. All received biological valves. Duration N/A - surgical procedure. Concurrent medication/care: All patients received aspirin (91mg) and clopidogrel (≥300mg) after the procedure and heparin during the procedure. Patients continued to take aspirin indefinitely and clopidogrel for a minimum of 1 month. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological (Appear to be biological based on details reported in the protocol).
Funding	Study funded by industry (Supported by Edwards lifesciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPLACEMENT WITH BIOLOGICAL VALVES versus STANDARD SURGERY REPLACEMENT WITH BIOLOGICAL VALVE

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 5 years; Group 1: 436/1011, Group 2: 370/1021
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91, Reason: Missing due to withdrawing or lost to follow-up.; Group 2 Number missing: 190, Reason: Missing due to withdrawing or lost to follow-up.
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 5 years; Group 1: Observed events 436 n=1011 ; Group 2: Observed events 370 n=1021; HR 1.09; Lower CI 0.95 to Upper CI 1.25
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91, Reason: Missing due to withdrawing or lost to follow-up.;

Group 2 Number missing: 190, Reason: Missing due to withdrawing or lost to follow-up.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Death from cardiac causes at 5 years; Group 1: 245/1011, Group 2: 223/1021
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91, Reason: Missing due to withdrawing or lost to follow-up.; Group 2 Number missing: 190, Reason: Missing due to withdrawing or lost to follow-up.
- Actual outcome for Aortic stenosis (non-bicuspid): Death from cardiac causes at 5 years; Group 1: Observed events 245 n=1011 ; Group 2: Observed events 223 n=1021; HR 1.02; Lower CI 0.85 to Upper CI 1.23
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91, Reason: Missing due to withdrawing or lost to follow-up.; Group 2 Number missing: 190, Reason: Missing due to withdrawing or lost to follow-up.

Protocol outcome 3: Interevention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 30 days; Group 1: 39/1011, Group 2: 41/1021
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 17 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.; Group 2 Number missing: 0, Reason: 77 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): KCCQ summary at 2 years; Group 1: mean 19.22 (SD 23.71); n=681, Group 2: mean 18.24 (SD 23.21); n=573; KCCQ summary 0-100 Top=High is good outcome; Comments: Change score compared with baseline. Higher value indicates better improvement in quality of life. Baseline values: TAVR, 53.2 (21.81, n=950); AVR, 52.98 (21.32, n=883)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar at baseline; Group 1 Number missing: 330; Group 2 Number missing: 448
- Actual outcome for Aortic stenosis (non-bicuspid): SF-36 physical summary at 2 years; Group 1: mean 2.992 (SD 9.719); n=668, Group 2: mean 2.716 (SD 10.48); n=558; SF-36 physical summary 0-100 Top=High is good outcome; Comments: Change compared to baseline so higher positive value indicates better improvement in quality of life. Baseline values: TAVR, 36.03 (8.911, n=950); AVR, 35.91 (8.755, n=883)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar at baseline; Group 1 Number missing: 343; Group 2 Number

missing: 433
- Actual outcome for Aortic stenosis (non-bicuspid): SF-36 mental summary at 2 years; Group 1: mean 2.28 (SD 12.66); n=668, Group 2: mean 2.858 (SD 12.36); n=588; SF-36 mental summary 0-100 Top=High is good outcome; Comments: Compared with baseline so higher positive values indicate a better improvement in quality of life. Baseline values: TAVR, 48.75 (11.32, n=950); SAVR, 47.69 (11.73, n=883)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar at baseline; Group 1 Number missing: 343; Group 2 Number missing: 433
- Actual outcome for Aortic stenosis (non-bicuspid): EQ-5D utilities at 2 years; Group 1: mean 0.025 (SD 0.188); n=677, Group 2: mean 0.028 (SD 0.198); n=569; EQ-5D utilities 0-1 Top=High is good outcome; Comments: Compared with baseline so higher positive value indicates better improvement in quality of life. Baseline values: TAVR, 0.748 (0.168, n=950); AVR, 0.732 (0.17, n=883)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar at baseline; Group 1 Number missing: 334; Group 2 Number missing: 452

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Any neurological event (including stroke and TIA) at 30 days; Group 1: 64/1011, Group 2: 65/1021
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 17 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.; Group 2 Number missing: 0, Reason: 77 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.

Protocol outcome 6: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Life threatening or disabling bleeding at 30 days; Group 1: 105/1011, Group 2: 442/1021
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 17 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.; Group 2 Number missing: 0, Reason: 77 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.

Protocol outcome 7: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Aortic valve reintervention at 5 years; Group 1: 21/1011, Group 2: 6/1021
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91, Reason: Missing due to withdrawing or lost to follow-up.; Group 2 Number missing: 190, Reason: Missing due to withdrawing or lost to follow-up.
- Actual outcome for Aortic stenosis (non-bicuspid): Aortic valve reintervention at 5 years; Group 1: Observed events 21 n=1011 ; Group 2: Observed events 6 n=1021; HR 3.28; Lower CI 1.32 to Upper CI 8.13
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91, Reason: Missing due to withdrawing or lost to follow-up.; Group 2 Number missing: 190, Reason: Missing due to withdrawing or lost to follow-up.

Protocol outcome 8: Length of hospital stay at after intervention
- Actual outcome for Aortic stenosis (non-bicuspid): Index hospitalisation at 30 days;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 17 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.; Group 2 Number missing: 0, Reason: 77 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.

Protocol outcome 9: Re-hospitalisation at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Rehospitalisation at 5 years; Group 1: 281/1011, Group 2: 209/1021
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91, Reason: Missing due to withdrawing or lost to follow-up.; Group 2 Number missing: 190, Reason: Missing due to withdrawing or lost to follow-up.
- Actual outcome for Aortic stenosis (non-bicuspid): Rehospitalisation at 5 years; Group 1: Observed events 281 n=1011 ; Group 2: Observed events 209 n=1021; HR 1.28; Lower CI 1.07 to Upper CI 1.53
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91, Reason: Missing due to withdrawing or lost to follow-up.; Group 2 Number missing: 190, Reason: Missing due to withdrawing or lost to follow-up.

Protocol outcome 10: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New permanent pacemaker at 30 days; Group 1: 85/1011, Group 2: 68/1021
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 17 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.; Group 2 Number missing: 0, Reason: 77 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they

use Kaplan-Meier estimates and so has not reported missing patients.

Protocol outcome 11: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New atrial fibrillation at 30 days; Group 1: 91/1011, Group 2: 265/1021
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 17 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.; Group 2 Number missing: 0, Reason: 77 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.

Protocol outcome 12: Prosthetic valve endocarditis at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Endocarditis at 5 years; Group 1: 30/1011, Group 2: 19/1021
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91, Reason: Missing due to withdrawing or lost to follow-up.; Group 2 Number missing: 190, Reason: Missing due to withdrawing or lost to follow-up.

Protocol outcome 13: Major vascular complications at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major vascular complications at 30 days; Group 1: 80/1011, Group 2: 51/1021; Comments: Kaplan Meier estimates
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 17 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.; Group 2 Number missing: 0, Reason: 77 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.

Protocol outcome 14: Renal failure at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): AKI at 30 days; Group 1: 13/1011, Group 2: 31/1021; Comments: Kaplan-Meier estimates
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 17 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they use Kaplan-Meier estimates and so has not reported missing patients.; Group 2 Number missing: 0, Reason: 77 patients did not receive the intervention mostly because they didn't want surgery after randomisation. However, they

use Kaplan-Meier estimates and so has not reported missing patients.	
Protocol outcomes not reported by the study	Onset or exacerbation of heart failure at ≥12 months

Study	Mächler 1999[229]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Austria; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Aortic stenosis (non-bicuspid)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients with requiring aortic valve intervention (from aortic valve index can tell this was severe aortic stenosis).
Exclusion criteria	Acute endocarditis, concomitant procedures and need for reoperation.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): Intervention: 65 (31-77), control: 65 (30-79). Interquartile range intervention: 65 (56-70). Interquartile range control: 65 (55-72). Gender (M:F): 71:49. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mostly below. Occasional patients above 75, but the interquartile range falls into the lower category.). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4.

	Operative risk (for AS and MR): Not stated / Unclear 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Ministernotomy replacement with biological or mechanical valve. L-shaped ministernotomy. Replacement with either CarboMedics (mechanical prosthesis), Mosaic bioprosthesis or Freestyle biprosthesis. Duration N/A - surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (No way of knowing the proportion of valve types from the information provided). (n=60) Intervention 2: Standard surgery replacement with biological or mechanical valves. Standard sternotomy. 90% of patients (54) received the CarboMedics mechanical prosthesis. 10% received either the Freestyle or Mosaic bioprosthesis. Duration N/A - Surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (Majority mechanical (90%).).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE versus STANDARD SURGERY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Mortality at 30 to 745 days; Group 1: 3/60, Group 2: 2/57; Comments: Taken from survival rate - 95% in group 1, 97% in group 2. Doesn't state the causes of death for the patients in the standard surgical replacement group and one patient in the ministernotomy group.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: not stated.

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Intervention related mortality (stroke) at 30 days; Group 1: 1/60, Group 2: 0/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Strokes (including 30-day mortality) at 30 days; Group 1: 1/60, Group 2: 0/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Reoperation for bleeding at 30 days; Group 1: 5/60, Group 2: 3/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Study does not report major bleeding that did not require reoperation, so downgraded for indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Reoperation for paravalvular leakage at 3 months; Group 1: 1/60, Group 2: 0/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Pacing wire implantation at 30 days; Group 1: 14/60, Group 2: 16/60; Comments: Ministernotomy: 8 ventricular pacing wires, 6 bifocal pacing wires. Standard sternotomy: 11 ventricular pacing wires, 5 bifocal pacing wires.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Supraventricular arrhythmias at 30 days; Group 1: 1/60, Group 2: 16/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Supraventricular tachycardia can include atrial fibrillation and atrial flutter. Therefore, downgraded for indirectness.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 8: Prosthetic valve endocarditis at ≥12 months - Actual outcome for Aortic stenosis (non-bicuspid): Endocarditis at 1 year; Group 1: 3/60, Group 2: 0/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Cardiac mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study (subsidiary papers)	Mack 2019[232] (Baron 2019[42], Pibarot 2020[294])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1000)
Countries and setting	Conducted in Australia, Canada, Japan, New Zealand, USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clear echocardiographic parameters
Stratum	Aortic stenosis (non-bicuspid)
Subgroup analysis within study	Not applicable:
Inclusion criteria	Adults with severe, calcific aortic stenosis who it has been agreed by a multidisclipinary team that they have an STS score of <4.
Exclusion criteria	Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath, evidence of acute MI within 1 month before randomisation, congenital bicuspid or unicuspid valve, non-calcified valve, severe aortic regurgitation, severe mitral regurgitation, clinical frailty as determined by heart team
Age, gender and ethnicity	Age - Mean (SD): Intervention: 73.3±5.8, Control: 73.6±6.1. Gender (M:F): 658:292. Ethnicity: Majority caucasian (83 patients of nonwhite race or ethnic group, 867 not in this group)
Further population details	1. Age: Mixed (Mean age with confidence intervals falls over the 75 year limit). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Low (By study design. STS score intervention: 1.9±0.7, STS score control: 1.9±0.6. EuroSCORE II intervention: 1.5±1.2,

	EuroSCORE II control: 1.5±0.9). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=503) Intervention 1: Transcatheter replacement with biological valves. TAVR with a SAPIEN 3 system. Transfemoral placement. Duration N/A - surgical procedure. Concurrent medication/care: Started on aspirin 81mg and clopidogrel (>300mg) before TAVR and advised to continue taking for at least 1 month. Concomitant procedures included: percutaneous coronary intervention(stenting and balloon angioplasty), 32/496 (6.5%); pacemaker or implantable cardioverter-defibrillator, 5/496 (1.0%); other, 2/496 (0.4%) – included one switched to surgery and received aortic root enlargement. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Transfemoral 2. Valve type: Biological (n=497) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological valve. 75.7% of patients had conventional surgical procedure. 24.3% had a minimally invasive procedure. Duration N/A - surgical procedure. Concurrent medication/care: Concomitant procedures included: coronary artery bypass grafting, 58/454 (12.8%); MAZE, 22/454 (4.8%) – includes MAZE, extended L atrial maze, extended L + R atrial maze and pulmonary vein isolation; left atrial appendage ligation, 43/454 (9.5%); root enlargement, 21/454 (4.6%); ascending aorta replacement, 1/454 (0.2%); aortic endarterectomy, 4/454 (0.9%); septal myomectomy, 4/454 (0.9%); replacement or repair for mitral valve regurgitation, 6/454 (1.3%); replacement or repair for tricuspid valve regurgitation, 4/454 (0.9%); other, 1/454 (0.2%). Indirectness: Serious indirectness; Indirectness comment: Includes patients that had a minimally invasive procedure. Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological
Funding	Study funded by industry (Edwards Lifesciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPLACEMENT WITH BIOLOGICAL VALVES versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL VALVE

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 1 year; Group 1: Observed events 5 n=496 ; Group 2: Observed events 11 n=454; HR 0.41; Lower CI 0.14 to Upper CI 1.17
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 1 year; Group 1: 5/496, Group 2: 11/454
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Cardiac mortality at 1 year; Group 1: 4/496, Group 2: 9/454; Comments: Based on Kaplan-Meier estimates
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.
- Actual outcome for Aortic stenosis (non-bicuspid): Cardiac mortality at 1 year; Group 1: Observed events 4 n=496 ; Group 2: Observed events 9 n=454; HR 0.4; Lower CI 0.12 to Upper CI 1.3; Advantage to research or control? R; Follow up details: 1 year
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

Protocol outcome 3: Interevention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Intervention-related mortality at 30 days; Group 1: 2/496, Group 2: 5/454; Comments: TAVR: 1 death due to annulus rupture (intra-procedural), 1 death due to LV perforation (intra-procedural). SAVR: 3 deaths due to PEA arrest, 1 death due to respirator failure, 1 death due to sepsis (GI ischaemia)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected

outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): KCCQ overall score at 1 year; Group 1: mean 19.4 (SD 18.9351); n=479, Group 2: mean 17.4 (SD 20.3466); n=400; KCCQ overall score 0-100 Top=High is good outcome; Comments: As-treated analysis rather than ITT. Baseline values: TAVR, 70.4 (19.4, n=494); and SAVR, 70.1 (20.9, n=449).
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 24, Reason: Exclusion criteria discovered after randomisation: 1; Withdrew: 7; missed visit: 2; no baseline health status data: 2; missing 1 year health status data: unclear.; Group 2 Number missing: 97, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 50; lost to follow-up: 1; missing baseline health status data: 6; missing 1 year health status data: unclear.
- Actual outcome for Aortic stenosis (non-bicuspid): SF-36 physical summary at 1 year; Group 1: mean 5.2 (SD 8.8167); n=469, Group 2: mean 5 (SD 8.0253); n=389; SF-36 physical 0-100 Top=High is good outcome; Comments: As-treated analysis rather than ITT. Baseline values: TAVR, 44.1 (9.2, n=494); and SAVR, 44.1 (9.0, n=449).
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 34, Reason: Exclusion criteria discovered after randomisation: 1; Withdrew: 7; missed visit: 2; no baseline health status data: 2; missing 1 year health status data: unclear.; Group 2 Number missing: 108, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 50; lost to follow-up: 1; missing baseline health status data: 6; missing 1 year health status data: unclear.
- Actual outcome for Aortic stenosis (non-bicuspid): SF-36 mental summary at 1 year; Group 1: mean 3.5 (SD 8.8544); n=473, Group 2: mean 4 (SD 9.0518); n=391; SF-36 mental 0-100 Top=High is good outcome; Comments: As-treated analysis rather than ITT. Baseline values: TAVR, 52.5 (9.1, n=494); and SAVR, 51.3 (10.0, n=449)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 30, Reason: Exclusion criteria discovered after randomisation: 1; Withdrew: 7; missed visit: 2; no baseline health status data: 2; missing 1 year health status data: unclear.; Group 2 Number missing: 106, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 50; lost to follow-up: 1; missing baseline health status data: 6; missing 1 year health status data: unclear.
- Actual outcome for Aortic stenosis (non-bicuspid): EQ-5D at 1 year; Group 1: mean 0.04 (SD 0.1109); n=475, Group 2: mean 0.04 (SD 0.2012); n=391; EQ-5D utilities 0-1 Top=High is good outcome; Comments: As-treated analysis rather than ITT. Baseline values: TAVR, 0.81 (0.11, n=494); and SAVR, 0.83 (0.13, n=449).
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected

outcomes; Group 1 Number missing: 28, Reason: Exclusion criteria discovered after randomisation: 1; Withdrew: 7; missed visit: 2; no baseline health status data: 2; missing 1 year health status data: unclear.; Group 2 Number missing: 106, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 50; lost to follow-up: 1; missing baseline health status data: 6; missing 1 year health status data: unclear.

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Any stroke at 30 days; Group 1: 3/496, Group 2: 11/454; Comments: Based on Kaplan-Meier estimates
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

Protocol outcome 6: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major bleeding at 30 days; Group 1: 13/496, Group 2: 61/454; Comments: Determined by Kaplan-Meier estimates
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

Protocol outcome 7: Length of hospital stay at after intervention
- Actual outcome for Aortic stenosis (non-bicuspid): Length of index hospitalisation at 30 days;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

Protocol outcome 8: Re-hospitalisation at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Rehospitalisation at 1 year; Group 1: Observed events 36 n=496 ; Group 2: Observed events 49 n=454; HR 0.65; Lower CI 0.42 to Upper CI 1
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

- Actual outcome for Aortic stenosis (non-bicuspid): Rehospitalisation at 1 year; Group 1: 36/496, Group 2: 49/454
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

Protocol outcome 9: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New permanent pacemaker at 30 days; Group 1: 32/496, Group 2: 18/454; Comments: Determined by Kaplan-Meier estimates
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

Protocol outcome 10: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New onset atrial fibrillation at 30 days; Group 1: 21/417, Group 2: 145/369; Comments: Determined by Kaplan-Meier estimates. Denominators are those that did not have AF at baseline.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6. Further 79 not included in analysis as they had AF at baseline.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35. Further 85 not included in analysis as they had AF at baseline.

Protocol outcome 11: Prosthetic valve endocarditis at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Endocarditis at 1 year; Group 1: 1/496, Group 2: 2/454; Comments: Determined by Kaplan-Meier estimates
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.

Protocol outcome 12: Major vascular complications at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major vascular complications at 30 days; Group 1: 10/496, Group 2: 6/454

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35. Protocol outcome 13: Renal failure at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): AKI at 30 days; Group 1: 7/496, Group 2: 39/454 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35. - Actual outcome for Aortic stenosis (non-bicuspid): AKI stage II/III at 30 days; Group 1: 2/496, Group 2: 8/454 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Differences in concomitant procedures received at surgery may have affected outcomes; Group 1 Number missing: 7, Reason: Exclusion criteria discovered after randomisation: 1. Withdrew: 6.; Group 2 Number missing: 43, Reason: Exclusion criteria discovered after randomisation: 8. Withdrew: 35.	
Protocol outcomes not reported by the study	Onset or exacerbation of heart failure at ≥12 months; Need for re-intervention at ≥12 months

Study	Malik 2015[236]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=281)
Countries and setting	Conducted in Pakistan; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: History, examination and routine laboratory tests - does not state if echocardiography was done. However, they had surgery so can confirm from that.
Stratum	Mixed/unclear mitral valve disease
Subgroup analysis within study	Not applicable
Inclusion criteria	All people who underwent mitral valve replacement according to the ACC/AHA guidelines
Exclusion criteria	People with incomplete data or loss of follow up before 1 year, people older than 80 years
Recruitment/selection of patients	All patients were from 1 centre recruited after discussion at a multidisciplinary team meeting
Age, gender and ethnicity	Age - Other: Mean age intervention = 26±12. Mean age control = 28±11. Gender (M:F): 73:208. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mean age intervention = 26±12. Mean age control =28±11.). 2. Childbearing age: Women of childbearing age (<45) (Mean age less than 45.). 3. Morphology (for MS): Not stated / Unclear 4. Operative risk (for AS and MR): Not stated / Unclear 5. Primary vs secondary valve disease (for MR and TR): Not stated / Unclear 6. Systolic dysfunction (for AR): Not applicable

Indirectness of population	Serious indirectness: Population unclear as to whether people had mitral regurgitation or mitral stenosis
Interventions	(n=77) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Right anterior thoracotomy replacement with biological or mechanical valve. Right anterolateral thoracotomy via the right submammary fold with access from the 4th intercostal space. Duration N/A - surgical intervention. Concurrent medication/care: Same anaesthetic regime as the other group. Received oral acenocoumarol post-op (INR target 2-2.5). Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear (n=204) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Standard median sternotomy approach. Duration N/A - surgical intervention. Concurrent medication/care: Same anaesthetic regime as the other group. Received oral acenocoumarol post-op (INR target 2-2.5). Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIGHT ANTERIOR THORACOTOMY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: Intervention-related mortality at 30 days
- Actual outcome for Mixed/unclear mitral valve disease: Mortality at Unclear - likely postoperative, but not stated clearly; Group 1: 4/77, Group 2: 14/204
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear time period of outcome and unclear type of mitral valve disease; Baseline details: Only reports age and sex, of which the sex reported is hugely different between the arms; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mixed/unclear mitral valve disease: CVA – assumed as cerebrovascular accident - likely during the immediate postoperative period; Group 1: 1/77, Group 2: 1/204
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear time period of outcome and unclear type of mitral valve disease; Baseline details: Only reports age and sex, of which the sex reported is hugely different between the arms; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Need for re-intervention at ≥12 months
- Actual outcome for Mixed/unclear mitral valve disease: Reopening - likely during the immediate postoperative period; Group 1: 0/77, Group 2: 10/204
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear time period of outcome and unclear type of mitral valve disease. Unclear what reopening refers to - may not be valve reintervention.; Baseline details: Only reports age and sex, of which the sex reported is hugely different between the arms; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Length of hospital stay at after intervention
- Actual outcome for Mixed/unclear mitral valve disease: Post op hospital stay at After intervention; Group 1: mean 5 days (SD 1); n=77, Group 2: mean 8.5 days (SD 1); n=204; Comments: Reports as +1 day rather than ±. Reported as: Intervention: 5+1; control: 8.5+1. Presented as mean with 2 standard deviations in the report.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Only reports age and sex, of which the sex reported is hugely different between the arms; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Prosthetic valve endocarditis at ≥12 months
- Actual outcome for Mixed/unclear mitral valve disease: Endocarditis at 2 years; Group 1: 1/69, Group 2: 2/190
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Only reports age and sex, of which the sex reported is hugely different between the arms; Group 1 Number missing: 8, Reason: 8 lost to follow up; Group 2 Number missing: 14, Reason: 14 lost to follow up

Protocol outcome 6: Renal failure at 30 days
- Actual outcome for Mixed/unclear mitral valve disease: Renal impairment at Unclear - likely during the immediate postoperative period; Group 1: 2/77, Group 2: 1/204

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear time period of outcome and unclear type of mitral valve disease; Baseline details: Only reports age and sex, of which the sex reported is hugely different between the arms; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Cardiac mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related major bleeding at 30 days; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Major vascular complications at 30 days

Study	Medved 2010[247]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Croatia; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Not clear: People had surgery and were followed up for the length of their initial hospital episode (on average 14.25 days)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients were known to have mitral insufficiency. Patients had intraoperative dynamic testing (echocardiography) to ensure correct severity for the study.
Stratum	Mitral regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	People older than 70 years with mitral valve insufficiency (grades III-IV)
Exclusion criteria	People with previous mitral valve surgical treatment, myocardial infarction within 7 days and younger than 70 years.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): MV repair: 76±5, MV replacement: 74.3±3. Gender (M:F): 65:15. Ethnicity: Not stated
Further population details	1. Age: Mixed (MV repair: 76±5, MV replacement: 74.3±3. No patients under the age of 70.). 2. Childbearing age: Women not of childbearing age (≥45 years) 3. Morphology (for MS): Not applicable 4. Operative risk (for

	AS and MR): High (Euro-score MV repair: 16.94%. Euro-score MV replacement: 15.76%). 5. Primary vs secondary valve disease (for MR and TR): Not stated / Unclear 6. Systolic dysfunction (for AR): Not applicable
Extra comments	.
Indirectness of population	Serious indirectness: 25 people required aortic valve replacement at the same time as mitral valve repair/replacement and 27 people required tricuspid valve annuloplasty.
Interventions	(n=40) Intervention 1: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Conventional median sternotomy and full cardiopulmonary bypass. Anterograde Calafiore cardioplegia followed with retrograde cardioplegia. Moderate systemic hypothermia was used. Valve type not stated. Duration N/A - Surgical procedure. Concurrent medication/care: Heparin was used as an anticoagulant during the procedure. Anaesthetic used propofol, midazolam, atracuronium and inhaled isoflurane. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear (n=40) Intervention 2: Standard surgery repair - Median sternotomy - repair. Conventional median sternotomy and full cardiopulmonary bypass. Anterograde Calafiore cardioplegia followed with retrograde cardioplegia. Moderate systemic hypothermia was used. Valve type not stated. Duration N/A - Surgical procedure. Concurrent medication/care: Heparin was used as an anticoagulant during the procedure. Anaesthetic used propofol, midazolam, atracuronium and inhaled isoflurane. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES versus MEDIAN STERNOTOMY - REPAIR

Protocol outcome 1: Cardiac mortality at ≥12 months
- Actual outcome for Mitral regurgitation: In-hospital death at During hospital admission (<30 days); Group 1: 1/40, Group 2: 2/40; Comments: Deaths in repair group: perioperative myocardial infarction (n=1) and multiorgan failure (n=1). Death in replacement group: rupture of ventricle in emphatically calcified posterior part of mitral valve annulus.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Follow-up <3 months; Baseline details: More women had mitral valve replacement than mitral valve repair (12 for MV replacement, 3 for MV repair).; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Mitral regurgitation: In-hospital death at During hospital admission (<30 days); Group 1: 1/40, Group 2: 2/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: More women had mitral valve replacement than mitral valve repair (12 for MV replacement, 3 for MV repair).; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral regurgitation: Neurologic dysfunction at During hospital admission (<30 days); Group 1: 1/40, Group 2: 1/40
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not clear if this is regarding stroke or a different form of neurological disorder; Baseline details: More women had mitral valve replacement than mitral valve repair (12 for MV replacement, 3 for MV repair).; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Need for re-intervention at ≥12 months
- Actual outcome for Mitral regurgitation: Reoperation at During hospital admission (<30 days); Group 1: 1/40, Group 2: 3/40; Comments: 1 reoperation stated in table 3 of study. Also mentions three in repair group that underwent replacement due to inadequate repair.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Follow-up <3 months; Baseline details: More women had mitral valve replacement than mitral valve repair (12 for MV replacement, 3 for MV repair).; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Length of hospital stay at after intervention
- Actual outcome for Mitral regurgitation: In-hospital stay at During hospital admission (<30 days); Group 1: mean 13.5 days (SD 0); n=40, Group 2: mean 15 days (SD 0); n=40; Comments: No standard deviation or range provided

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: More women had mitral valve replacement than mitral valve repair (12 for MV replacement, 3 for MV repair).; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related major bleeding at 30 days; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study	**Momtahen 1997[255]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=577)
Countries and setting	Conducted in Iran; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Not clear: At least for their hospital stay. However, unclear how long this is.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Mitral stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Severe rheumatic mitral stenosis (assessed by echocardiography)
Exclusion criteria	More than mild mitral regurgitation, left atrial thrombus on imaging
Recruitment/selection of patients	No additional information given - patients recruited from the one centre the trial took place at
Age, gender and ethnicity	Age - Mean (range): 32 (15-55). Gender (M:F): 126:451. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mean age: 32 (15-55)). 2. Childbearing age: Women of childbearing age (<45) (The majority of the cohort are women with a mean age of 32). 3. Morphology (for MS): Morphology suitable for transcatheter intervention 4. Operative risk (for AS and MR): Not applicable 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable

Indirectness of population	Serious indirectness: Includes patients under the age of 18
Interventions	(n=450) Intervention 1: Transcatheter repair. Balloon commissurotomy - transseptal approach with a single balloon (Inoue balloon catheter - 24-30mm balloon). Duration N/A - surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Not applicable (n=127) Intervention 2: Minimally invasive surgery repair - Non-sternotomy repair. Surgical closed commissurotomy - performed by standard left lateral thoracotomy with a Tubbs dilator inserted via a left ventriculotomy. Duration N/A - surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus NON-STERNOTOMY REPAIR

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral stenosis: Mortality at Unclear; Group 1: 0/127, Group 2: 1/127
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Very significant risk of bias as they do not report outcomes for a substantial number of participants.; Indirectness of outcome: Serious indirectness, Comments: Likely <3 months follow-up; Baseline details: Reports a limited number of parameters and has difference in some of the parameters reported (NYHA class, atrial fibrillation). Does not fully report some parameters (ex. mitral valve morphologic score, mitral valve calcification).; Group 1 Number missing: 323, Reason: No reason given; Group 2 Number missing: 0

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral stenosis: Mortality at Unclear; Group 1: 0/127, Group 2: 0/127
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Very significant risk of bias as they do not report outcomes for a substantial number of participants.; Indirectness of

outcome: Serious indirectness, Comments: Likely <3 months follow-up; Baseline details: Reports a limited number of parameters and has difference in some of the parameters reported (NYHA class, atrial fibrillation). Does not fully report some parameters (ex. mitral valve morphologic score, mitral valve calcification).; Group 1 Number missing: 323, Reason: No reason given; Group 2 Number missing: 0 Protocol outcome 3: Intervention-related mortality at 30 days - Actual outcome for Mitral stenosis: Mortality at Unclear; Group 1: 0/127, Group 2: 1/127; Comments: 1 death in control arm due to infection Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Very significant risk of bias as they do not report outcomes for a substantial number of participants.; Indirectness of outcome: No indirectness ; Baseline details: Reports a limited number of parameters and has difference in some of the parameters reported (NYHA class, atrial fibrillation). Does not fully report some parameters (ex. mitral valve morphologic score, mitral valve calcification).; Group 1 Number missing: 323, Reason: No reason given; Group 2 Number missing: 0 Protocol outcome 4: Intervention-related stroke or TIA at 30 days - Actual outcome for Mitral stenosis: Thromboembolism at Unclear; Group 1: 0/127, Group 2: 0/127 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Very significant risk of bias as they do not report outcomes for a substantial number of participants.; Indirectness of outcome: No indirectness; Baseline details: Reports a limited number of parameters and has difference in some of the parameters reported (NYHA class, atrial fibrillation). Does not fully report some parameters (ex. mitral valve morphologic score, mitral valve calcification).; Group 1 Number missing: 323, Reason: No reason given; Group 2 Number missing: 0 Protocol outcome 5: Need for re-intervention at ≥12 months - Actual outcome for Mitral stenosis: Valve replacement following development of severe mitral regurgitation at Unclear; Group 1: 4/127, Group 2: 3/127; Comments: n=2 valve replacements in each group. n=2 and n=1 open mitral valve commissurotomy in transcatheter and surgical repair groups, respectively. Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Very significant risk of bias as they do not report outcomes for a substantial number of participants.; Indirectness of outcome: Serious indirectness, Comments: Follow-up likely <3 months; Baseline details: Reports a limited number of parameters and has difference in some of the parameters reported (NYHA class, atrial fibrillation). Does not fully report some parameters (ex. mitral valve morphologic score, mitral valve calcification).; Group 1 Number missing: 323, Reason: No reason given; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related major bleeding at 30 days; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months;

Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days	

Study	Moustafa 2007[258]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	60 (n=1)
Countries and setting	Conducted in Egypt; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Not clear: Postoperative until end of hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Mixed/unclear aortic valve disease: 50% have aortic stenosis, 50% have aortic regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing first-time elective aortic valve replacement (50% had aortic stenosis, 50% had aortic regurgitation)
Exclusion criteria	Emergency operations, depressed left ventricular function (<25%), a heavily calcified ascending aorta, redo valve surgery, and aortic valve replacement associated with other valve lesions.
Recruitment/selection of patients	Consecutive patients at one centre
Age, gender and ethnicity	Age - Mean (SD): Intervention: 23.83±3.49, control: 22.93±2.35. Gender (M:F): 31:29. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Childbearing age: Women of childbearing age (<45) 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear 5. Primary vs secondary valve disease (for

	MR and TR): Not applicable 6. Systolic dysfunction (for AR): No systolic dysfunction (Ejection fraction intervention: 55±2.55%, control: 56±2.32%).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Ministernotomy replacement with mechanical valve. Reversed L-shaped ministernotomy from the sternal notch to the 3rd intercostal space. Duration N/A - surgical procedure. Concurrent medication/care: Anaesthetic regime: Etomidate (0.2-0.6 micrograms/kg), fentanyl (1-10 micrograms/kg), pancuronium (80 micrograms/kg) and propofol infusion (100-300 micrograms/kg/hr) for maintenance. Analgesia: Tenoxicam 4g/12 hours while in ITU. Oral paracetamol (500mg) while on the ward. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mechanical (n=30) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with mechanical valve. Median sternotomy. Duration N/A - surgical procedure. Concurrent medication/care: Anaesthetic regime: Etomidate (0.2-0.6 micrograms/kg), fentanyl (1-10 micrograms/kg), pancuronium (80 micrograms/kg) and propofol infusion (100-300 micrograms/kg/hr) for maintenance. Analgesia: Tenoxicam 4g/12 hours while in ITU. Oral paracetamol (500mg) while on the ward. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mechanical
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPLACEMENT WITH MECHANICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH MECHANICAL VALVE

Protocol outcome 1: Length of hospital stay at after intervention

- Actual outcome for Mixed/unclear aortic valve disease: Hospital stay at After intervention; Group 1: mean 8 days (SD 0.83); n=30, Group 2: mean 17.7 days (SD 8.7); n=30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Intervention-related mortality at 30 days; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Intervention-related major bleeding at 30 days; Need for re-intervention at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study	Nair 2018[263]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=222)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Mixed/unclear aortic valve disease: Aortic valve disease, type not specified
Subgroup analysis within study	Not applicable:
Inclusion criteria	Adults undergoing first-time isolated aortic valve replacement
Exclusion criteria	Emergency aortic valve replacement; LVEF≤30%; chest wall deformities; severe COPD (FEV1 or TLCO <40% predicted); BMI >35kg/m²; concomitant cardiac surgery; redo-surgery and inability to perform TOE.
Recruitment/selection of patients	People at a single centre
Age, gender and ethnicity	Age - Mean (SD): Intervention: 71.3 (12.3). Control: 72.1 (10.9). Gender (M:F): 112:110. Ethnicity: Not stated
Further population details	1. Age: Mixed (Intervention: 71.3 (12.3). Control: 72.1 (10.9).). 2. Childbearing age: Women not of childbearing age (≥45 years) (Given mean age). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Intermediate (Intervention: 5.9 (2.1). Control: 6.1 (2.1).). 5. Primary vs secondary valve disease

	(for MR and TR): Not applicable 6. Systolic dysfunction (for AR): No systolic dysfunction (Significant systolic dysfunction was an exclusion criteria).
Indirectness of population	Serious indirectness: Type of aortic valve disease unclear
Interventions	(n=118) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Ministernotomy replacement with biological or mechanical valve. Skin incised from half-way between the suprasternal notch and the sternal angle to the level of the fourth intercostal space, measuring approximately 8cm. The manubrium was divided in the midline from the suprasternal notch inferiorly and then into the right fourth intercostal space. The aortic valve prosthesis function was confirmed by transoesophageal echocardiography. The aorta was cannulated using a single wired flexible aortic cannula. Duration N/A - surgical procedure. Concurrent medication/care: Loading dose of 300 units/kg heparin followed by boluses of 5000 units to achieve an activated clotting time above 450s. No other information given. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear (n=104) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Skin incised between the suprasternal notch and the xiphoid process and the sternum was divided at the midline between these landmarks. A two-stage venous cannula was used for atrial cannulation. Duration N/A - surgical procedure. Concurrent medication/care: Loading dose of 300 units/kg heparin followed by boluses of 5000 units to achieve an activated clotting time above 450s. No other information given. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear
Funding	Academic or government funding (Supported by the National Institute for Health Research (NIHR))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES	

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: All-cause mortality at 12 months; Group 1: 12/105, Group 2: 7/86
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 1 ineligible for the trial. 1 needed full sternotomy for procedure. 4 unable to have a transoesophageal echo post-randomisation. 2 correct equipment unavailable. At 6 weeks: 3 lost to follow up, 6 missing. At 6 months: 4 additional lost to follow up. 6 missing. At 12 months: 1 additional lost to follow up. 5 missing.; Group 2 Number missing: 18, Reason: 1 withdrew before procedure. At 6 weeks: 3 lost to follow up, 4 missing. At 6 months: 2 additional lost to follow up, 4 missing. At 1 year: 1 additional lost to follow up, 12 missed.
- Actual outcome for Mixed/unclear aortic valve disease: All-cause mortality at 12 months; Group 1: Observed events 7 n=105 ; Group 2: Observed events 12 n=86; HR 1.871; Lower CI 0.723 to Upper CI 4.844; Log rank variance: 0.1966
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 1 ineligible for the trial. 1 needed full sternotomy for procedure. 4 unable to have a transoesophageal echo post-randomisation. 2 correct equipment unavailable. At 6 weeks: 3 lost to follow up, 6 missing. At 6 months: 4 additional lost to follow up. 6 missing. At 12 months: 1 additional lost to follow up. 5 missing.; Group 2 Number missing: 18, Reason: 1 withdrew before procedure. At 6 weeks: 3 lost to follow up, 4 missing. At 6 months: 2 additional lost to follow up, 4 missing. At 1 year: 1 additional lost to follow up, 12 missed.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: Cardiac mortality at 12 months; Group 1: 8/105, Group 2: 3/86
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 1 ineligible for the trial. 1 needed full sternotomy for procedure. 4 unable to have a transoesophageal echo post-randomisation. 2 correct equipment unavailable. At 6 weeks: 3 lost to follow up, 6 missing. At 6 months: 4 additional lost to follow up. 6 missing. At 12 months: 1 additional lost to follow up. 5 missing.; Group 2 Number missing: 18, Reason: 1 withdrew before procedure. At 6 weeks: 3 lost to follow up, 4 missing. At 6 months: 2 additional lost to follow up, 4 missing. At 1 year: 1 additional lost to follow up, 12 missed.

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Intervention-related mortality at 6 weeks; Group 1: 4/106, Group 2: 1/104
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: At a time period longer than 30 days; Group 1 Number missing: 9, Reason: 1 ineligible for the trial. 1 needed full sternotomy for procedure. 4 unable to have a transoesophageal echo post-randomisation. 2 correct equipment unavailable. At 6 weeks: 3 lost to follow up, 6 missing, 4 died.; Group 2 Number missing: 7, Reason: 1 withdrew before procedure. At 6 weeks:

3 lost to follow up, 4 missing. 1 died.

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: EQ-5D at 12 months; Group 1: mean 0.83 (SD 0.29); n=103, Group 2: mean 0.78 (SD 0.28); n=84; EQ-5D 0-1 Top=High is good outcome; Comments: Baseline intervention: 0.77 (0.19). Baseline control: 0.70 (0.24).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Reported in table; Group 2 Number missing: 20, Reason: Reported in table
- Actual outcome for Mixed/unclear aortic valve disease: SF-36 Bodily pain at 12 months; Group 1: mean 76 (SD 31); n=99, Group 2: mean 72 (SD 32); n=86; SF-36 Bodily pain subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 70 (25). Baseline control: 64 (28).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Reported in table; Group 2 Number missing: 18, Reason: Reported in table
- Actual outcome for Mixed/unclear aortic valve disease: SF-36 General health at 12 months; Group 1: mean 68 (SD 26); n=100, Group 2: mean 62 (SD 26); n=86; SF-36 General health subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 62 (20). Baseline control: 58 (22).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 18, Reason: Reported in table; Group 2 Number missing: 18, Reason: Reported in table
- Actual outcome for Mixed/unclear aortic valve disease: SF-36 Mental health at 12 months; Group 1: mean 76 (SD 26); n=100, Group 2: mean 73 (SD 23); n=86; SF-36 Mental Health subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 74 (18). Baseline control: 67 (21).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 18, Reason: Reported in table; Group 2 Number missing: 18, Reason: Reported in table
- Actual outcome for Mixed/unclear aortic valve disease: SF-36 Physical functioning at 12 months; Group 1: mean 74 (SD 30); n=100, Group 2: mean 67 (SD 31); n=86; SF-36 Physical functioning subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 54 (26). Baseline control: 47 (28).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 18, Reason: Reported in table; Group 2 Number missing: 18, Reason: Reported in table
- Actual outcome for Mixed/unclear aortic valve disease: SF-36 Role emotional at 12 months; Group 1: mean 76 (SD 39); n=98, Group 2: mean 71 (SD 42); n=85; SF-36 Role emotional subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 67 (40). Baseline control: 55 (46).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Reported in table; Group 2 Number

missing: 19, Reason: Reported in table
- Actual outcome for Mixed/unclear aortic valve disease: SF-36 Role physical at 12 months; Group 1: mean 64 (SD 44); n=98, Group 2: mean 52 (SD 46); n=85; SF-36 Role physical subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 33 (41). Baseline control: 23 (38).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Reported in table; Group 2 Number missing: 19, Reason: Reported in table
- Actual outcome for Mixed/unclear aortic valve disease: SF-36 Social functioning at 12 months; Group 1: mean 81 (SD 30); n=98, Group 2: mean 78 (SD 30); n=85; SF-36 Social functioning subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 66 (30). Baseline control: 61 (29).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Reported in table; Group 2 Number missing: 19, Reason: Reported in table
- Actual outcome for Mixed/unclear aortic valve disease: SF-36 Vitality at 12 months; Group 1: mean 60 (SD 26); n=100, Group 2: mean 54 (SD 26); n=86; SF-36 Vitality subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 46 (25). Baseline control: 40 (23).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 18, Reason: Reported in table; Group 2 Number missing: 18, Reason: Reported in table

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Stroke at 12 months; Group 1: 2/98, Group 2: 3/82
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Reported over 12 months. Only reporting stroke (not TIA).; Group 1 Number missing: 20, Reason: 1 ineligible for the trial. 1 needed full sternotomy for procedure. 4 unable to have a transoesophageal echo post-randomisation. 2 correct equipment unavailable. At 6 weeks: 3 lost to follow up, 6 missing, 4 died. At 6 months: 4 additional lost to follow up. 6 missing. At 12 months: 1 additional lost to follow up. 5 missing. 3 additional deaths.; Group 2 Number missing: 22, Reason: 1 withdrew before procedure. At 6 weeks: 3 lost to follow up, 4 missing. 1 died. At 6 months: 2 additional lost to follow up, 4 missing. 1 additional death. At 1 year: 1 additional lost to follow up, 12 missed. 2 additional deaths.

Protocol outcome 6: Need for re-intervention at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: Reoperation at 1 year; Group 1: 6/98, Group 2: 2/82
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: 1 ineligible for the trial. 1 needed full sternotomy for procedure. 4 unable to have a transoesophageal echo post-randomisation. 2 correct equipment unavailable. At 6 weeks: 3 lost to follow

up, 6 missing, 4 died. At 6 months: 4 additional lost to follow up. 6 missing. At 12 months: 1 additional lost to follow up. 5 missing. 3 additional deaths.; Group 2 Number missing: 22, Reason: 1 withdrew before procedure. At 6 weeks: 3 lost to follow up, 4 missing. 1 died. At 6 months: 2 additional lost to follow up, 4 missing. 1 additional death. At 1 year: 1 additional lost to follow up, 12 missed. 2 additional deaths. Protocol outcome 7: Length of hospital stay at after intervention - Actual outcome for Mixed/unclear aortic valve disease: Time to discharge at After intervention; Group 1: mean 9.5 days (SD 6.5); n=118, Group 2: mean 8.6 days (SD 5.1); n=104; Comments: Produced by Kaplan-Meier estimation. Reports mean and standard error: Mini-sternotomy: 9.5 (0.6), full sternotomy 8.6 (0.5) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: Estimated from Kaplan Meier estimates. 1 ineligible for the trial. 1 needed full sternotomy for procedure. 4 unable to have a transoesophageal echo post-randomisation. 2 correct equipment unavailable.; Group 2 Number missing: 1, Reason: Estimated from Kaplan Meier estimates. 1 withdrew before procedure. Protocol outcome 8: Major vascular complications at 30 days - Actual outcome for Mixed/unclear aortic valve disease: Vascular serious adverse events at 1 year; Group 1: 1/98, Group 2: 9/82 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Recorded at 1 year; Group 1 Number missing: 20, Reason: 1 ineligible for the trial. 1 needed full sternotomy for procedure. 4 unable to have a transoesophageal echo post-randomisation. 2 correct equipment unavailable. At 6 weeks: 3 lost to follow up, 6 missing, 4 died. At 6 months: 4 additional lost to follow up. 6 missing. At 12 months: 1 additional lost to follow up. 5 missing. 3 additional deaths.; Group 2 Number missing: 22, Reason: 1 withdrew before procedure. At 6 weeks: 3 lost to follow up, 4 missing. 1 died. At 6 months: 2 additional lost to follow up, 4 missing. 1 additional death. At 1 year: 1 additional lost to follow up, 12 missed. 2 additional deaths.
Protocol outcomes not reported by the study	Onset or exacerbation of heart failure at ≥12 months; Intervention-related major bleeding at 30 days; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Renal failure at 30 days

Study (subsidiary papers)	Nasso 2014[266] (Speziale 2011[364])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Mitral regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Isolated, severe mitral regurgitation with an indication for elective reparative surgery on the basis of current guidelines. The aetiology of mitral regurgitation had to be represented by Barlow disease (bileaflet prolapse) of the mitral valve, on the basis of preoperative echocardiography, informed consent, no contraindication to mitral surgery, right minithoracotomy or peripheral cannulation. Patients were candidates for their primary cardiac operation.
Exclusion criteria	People with other concomitant cardiac disorders (coronary disease any more than mild valvular disease including mitral stenosis, tricuspid regurgitation graded >2/4, congenital heart defects and aortic disease).
Recruitment/selection of patients	No additional information available
Age, gender and ethnicity	Age - Other: Mean intervention: 53.9±10.6, Mean control: 54.3±10.5. Gender (M:F): 91:69. Ethnicity: Not stated

Further population details	1. Age: <75 years (Mean intervention: 53.9±10.6, Mean control: 54.3±10.5). 2. Childbearing age: Mixed 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear 5. Primary vs secondary valve disease (for MR and TR): Not stated / Unclear 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Minimally invasive surgery repair - Ministernotomy repair. Minithoracotomy (right anterolateral) in the inframammary groove (third intercostal space, working port). Instrument port at the 5th-7th intercostal space. Duration N/A - Surgical procedure. Concurrent medication/care: IV ketorolac 30mg each day until the fourth postoperative day. Then oral indomethacin, 50mg twice a day subsequently. No additional information available. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not applicable (n=80) Intervention 2: Standard surgery repair - Median sternotomy - repair. Conventional full median sternotomy with ascending aortic and bicaval cannulation. Duration N/A - surgical procedure. Concurrent medication/care: IV ketorolac 30mg each day until the fourth postoperative day. Then oral indomethacin, 50mg twice a day subsequently. No additional information available. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPAIR versus MEDIAN STERNOTOMY - REPAIR

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral regurgitation: Overall mortality at end of follow up at 3 years; Group 1: 3/79, Group 2: 3/80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: 1 lost to follow-up

Protocol outcome 2: Intervention-related mortality at 30 days

- Actual outcome for Mitral regurgitation: Operative mortality at Early postoperatively - likely <30 days; Group 1: 2/80, Group 2: 2/80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Quality of life at ≥12 months
- Actual outcome for Mitral regurgitation: SF-36 physical activity at 3 years; Group 1: mean 79.1 (SD 9.2); n=76, Group 2: mean 79.7 (SD 8.5); n=77; Comments: Baseline intervention: 53.8±5; Baseline control: 54.4±6

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 died. 2 lost to follow up - no reason given; Group 2 Number missing: 3, Reason: 3 died
- Actual outcome for Mitral regurgitation: SF-36 role limitation at 3 years; Group 1: mean 78.5 (SD 9); n=76, Group 2: mean 79.5 (SD 10.2); n=77; SF-36 Role limitation 0-100 Top=High is good outcome; Comments: Baseline intervention: 52.6±8.1; Baseline control: 52.1±7.6

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 died. 2 lost to follow up - no reason given; Group 2 Number missing: 3, Reason: 3 died
- Actual outcome for Mitral regurgitation: SF-36 general health at 3 years; Group 1: mean 82.9 (SD 9.7); n=76, Group 2: mean 84.2 (SD 8.7); n=77; SF-36 general health subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 51.3±6.2; Baseline control: 54.4±6

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 died. 2 lost to follow up - no reason given; Group 2 Number missing: 3, Reason: 3 died
- Actual outcome for Mitral regurgitation: SF-36 vitality at 3 years; Group 1: mean 79.8 (SD 8.6); n=76, Group 2: mean 78.8 (SD 8.2); n=77; SF-36 vitality subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 60.3±3.9; Baseline control: 59.6±4.3
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 died. 2 lost to follow up - no reason given; Group 2 Number

missing: 3, Reason: 3 died
- Actual outcome for Mitral regurgitation: SF-36 social activities at 3 years; Group 1: mean 84.2 (SD 7); n=76, Group 2: mean 83.8 (SD 7); n=77; SF-36 social activities subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 75.7±5.5; Baseline control: 76.2±6.1
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 died. 2 lost to follow up - no reason given; Group 2 Number missing: 3, Reason: 3 died
- Actual outcome for Mitral regurgitation: SF-36 mental health at 3 years; Group 1: mean 82.4 (SD 9.3); n=76, Group 2: mean 81.5 (SD 8.9); n=77; SF-36 mental health subscale 0-100 Top=High is good outcome; Comments: Baseline intervention: 76.8±7; Baseline control: 76.2±6.1
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 died. 2 lost to follow up - no reason given; Group 2 Number missing: 3, Reason: 3 died

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral regurgitation: Neurological complications at 30 days; Group 1: 1/70, Group 2: 2/70; Comments: Taken from the Speziale study - only recruited 140 patients in the study at this point. In the Nasso study they recruited additional people to increase the numbers after finding out that great participant numbers were required to provide adequate power to the study.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: May not all be stroke/TIA-related; Group 1 Number missing: 10, Reason: 10 participants recruited after the initial results were reported; Group 2 Number missing: 10, Reason: 10 participants recruited after the initial results were reported

Protocol outcome 5: Intervention-related major bleeding at 30 days
- Actual outcome for Mitral regurgitation: Reoperation due to bleeding at 30 days; Group 1: 4/70, Group 2: 3/70; Comments: Taken from the Speziale study - only recruited 140 patients in the study at this point. In the Nasso study they recruited additional people to increase the numbers after finding out that great participant numbers were required to provide adequate power to the study.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: 10 participants recruited after the initial results were reported; Group 2 Number missing: 10, Reason: 10 participants recruited after the initial results were reported

Protocol outcome 6: Need for re-intervention at ≥12 months
- Actual outcome for Mitral regurgitation: Mitral reoperation at 3 years; Group 1: 2/76, Group 2: 1/77
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 lost to follow up - no reason given; Group 2 Number missing: 0

Protocol outcome 7: Length of hospital stay at after intervention - Actual outcome for Mitral regurgitation: Length of hospital stay at After intervention; Group 1: mean 8.5 days (SD 4.5); n=80, Group 2: mean 11.6 days (SD 5); n=80; Comments: Reported values: Intervention - 8.5±4.5 days; Control - 11.6±5 days Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 8: Prosthetic valve endocarditis at ≥12 months - Actual outcome for Mitral regurgitation: Valve endocarditis at 3 years; Group 1: 0/76, Group 2: 0/77 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not technically prosthetic valve endocarditis as these are repair procedures?; Group 1 Number missing: 3, Reason: 3 deaths; Group 2 Number missing: 4, Reason: 1 lost to follow-up, 3 deaths Protocol outcome 9: Renal failure at 30 days - Actual outcome for Mitral regurgitation: Postoperative renal failure (increase in serum creatinine by >2mg/dL compared to baseline) at 30 days; Group 1: 3/70, Group 2: 3/70; Comments: Taken from the Speziale study - only recruited 140 patients in the study at this point. In the Nasso study they recruited additional people to increase the numbers after finding out that great participant numbers were required to provide adequate power to the study. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: 10 participants recruited after the initial results were reported; Group 2 Number missing: 10, Reason: 10 participants recruited after the initial results were reported	
Protocol outcomes not reported by the study	Cardiac mortality at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Major vascular complications at 30 days

Study (subsidiary papers)	Nielsen 2012[272] (Rex 2016[313])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=59); n=72 randomised
Countries and setting	Conducted in Denmark; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clearly stated echocardiographic parameters and assessment
Stratum	Aortic stenosis (non-bicuspid)
Subgroup analysis within study	Not applicable
Inclusion criteria	Significant valvular aortic stenosis (valve area <1cm^2), age initially greater than 70 but later increased to greater than 75, condition accessible both by SAVR and a-TAVI, expected survival >1 year following successful treatment, patient acceptance of participation in study as well as in the scheduled follow-up investigations
Exclusion criteria	Coronary artery disease to be treated by PCI or CABG, previous MI, previous PCI within 12 months, the need for other heart surgery, previous heart surgery, emergency surgery, unstable cardiac condition (requiring an assist device, inotropes or IV nitrates in operating room), ongoing infection requiring antibiotics, stroke within one month, reduced pulmonary function (FEV1 <11 or <40% expected), renal failure to be treated by haemodialysis, allergy to acetylsalicylic acid, clopidogrel, prasugrel or x-ray contrast material
Recruitment/selection of patients	Not stated

Age, gender and ethnicity	Age - Mean (SD): Intervention: 80±3.6, Control: 82±4.4. Gender (M:F): 21:49. Ethnicity: Not stated
Further population details	1. Age: 75 years or over 2. Childbearing age: Women not of childbearing age (≥45 years) (Based on mean age). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Low (Stated in paper. Logistic EuroSCORE intervention: 9.4±3.9, Logistic EuroSCORE control: 10.3±5.8, STS score intervention: 3.1±1.5, STS score control: 3.4±1.2). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Transcatheter replacement with biological valves. Edwards SAPIEN valve. Transapical route. Duration N/A - Surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Transapical 2. Valve type: Biological (n=36) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological valve. PERIMOUNT aortic heart valve (bioprosthetic). Duration N/A - Surgical procedure. Concurrent medication/care: None stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological
Funding	Other author(s) funded by industry (Two authors were part time proctors for Edwards Lifesciences.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPLACEMENT WITH BIOLOGICAL VALVES versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL VALVE

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Mortality at 5 years; Group 1: 4/29, Group 2: 7/29; Comments: Long term values taken from Rex study. This only reports patients from one of the two sites where the trial took place.
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Was originally reported as survival rate. Analysed to determine mortality.;

Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 12, Reason: The second study only includes patients at their treatment site. 30/36 originally randomised to this group were within this treatment site - 1 of these withdrew consent and 5 crossed over to the other group.; Group 2 Number missing: 8, Reason: The second study only includes patients at their treatment site - 29/36 originally randomised to this group were within this treatment site - 1 crossed over to the other group.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Mortality at 5 years; Group 1: 2/29, Group 2: 2/29; Comments: Long term values taken from Rex study. This only reports patients from one of the two sites where the trial took place. Deaths in transcatheter group included one on the waiting list and another due to coronary artery obstruction. Deaths in surgery group included one due to acute coronary syndrome and one due to cardiac arrest.
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Was originally reported as survival rate. Analysed to determine mortality.; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 12, Reason: The second study only includes patients at their treatment site. 30/36 originally randomised to this group were within this treatment site - 1 of these withdrew consent and 5 crossed over to the other group; Group 2 Number missing: 8, Reason: The second study only includes patients at their treatment site - 29/36 originally randomised to this group were within this treatment site - 1 crossed over to the other group.

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Mortality at 30 days; Group 1: 2/34, Group 2: 0/36; Comments: Taken from the Nielsen paper, including everybody apart from 1 patient who declined the trial and another who unexpectedly met exclusion criterion of impaired pulmonary function.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 2, Reason: 1 patient unexpectedly met exclusion criterion of impaired pulmonary function. 1 removed consent.; Group 2 Number missing: 0

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): SF-36 composite physical score at 5 years; Group 1: mean 37 (SD 10); n=29, Group 2: mean 42 (SD 10); n=29; SF-36 0-100 Top=High is good outcome; Comments: baseline intervention = 34±10, baseline control = 37±12
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 12, Reason: The second study only includes patients at their treatment site. 30/36 originally randomised to this group were within this treatment site - 1 of these withdrew consent and 5 crossed over to the other group; Group 2 Number missing: 8, Reason: The second study only includes patients at their treatment site - 29/36 originally randomised to this group were within this treatment

site - 1 crossed over to the other group.
- Actual outcome for Aortic stenosis (non-bicuspid): SF-36 composite mental score at 5 years; Group 1: mean 49 (SD 12); n=29, Group 2: mean 44 (SD 11); n=29; SF-36 0-100 Top=High is good outcome; Comments: Intervention baseline: 46±12, control baseline: 44±18
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 12, Reason: The second study only includes patients at their treatment site. 30/36 originally randomised to this group were within this treatment site - 1 of these withdrew consent and 5 crossed over to the other group; Group 2 Number missing: 8, Reason: The second study only includes patients at their treatment site - 29/36 originally randomised to this group were within this treatment site - 1 crossed over to the other group.

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major stroke or TIA at 30 days; Group 1: 3/34, Group 2: 1/36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 2, Reason: 1 patient died while on the waiting list. 1 removed consent.; Group 2 Number missing: 0

Protocol outcome 6: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Bleeding (requiring reintervention) at 30 days; Group 1: 1/34, Group 2: 1/36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 2, Reason: 1 patient died while on the waiting list. 1 removed consent.; Group 2 Number missing: 0

Protocol outcome 7: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Need for reintervention at 30 days; Group 1: 8/34, Group 2: 1/36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: reported at 30 day time-point only; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 2, Reason: 1 patient died while on the waiting list. 1 removed consent.; Group 2 Number missing: 0

Protocol outcome 8: Length of hospital stay at after intervention

- Actual outcome for Aortic stenosis (non-bicuspid): Mean hospital stay at 30 days; Group 1: mean 8.8 Days (SD 6.7); n=34, Group 2: mean 7.6 Days (SD 2.4); n=36 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 2, Reason: 1 patient died while on the waiting list. 1 removed consent.; Group 2 Number missing: 0 Protocol outcome 9: Intervention-related pacemaker implantation at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): Permanent pacemaker insertion at 30 days; Group 1: 2/34, Group 2: 1/36 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 2, Reason: 1 patient died while on the waiting list. 1 removed consent.; Group 2 Number missing: 0 Protocol outcome 10: Major vascular complications at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): Major vascular complications at 30 days; Group 1: 7/34, Group 2: 2/36 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 2, Reason: 1 patient died while on the waiting list. 1 removed consent.; Group 2 Number missing: 0 Protocol outcome 11: Renal failure at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): Need for dialysis at 30 days; Group 1: 1/34, Group 2: 0/36 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Aortic valve peak gradient was significantly lower for the SAVR group. But otherwise ok (including aortic valve area).; Group 1 Number missing: 2, Reason: 1 patient died while on the waiting list. 1 removed consent.; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Onset or exacerbation of heart failure at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months

Study (subsidiary papers)	Obadia 2018[274] (Obadia 2015[273], Iung 2019[171])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=307)
Countries and setting	Conducted in France; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Mitral regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >18 years, severe secondary mitral regurgitation characterised by echocardiogram (regurgitation volume >30mL/beat or a regurgitant orifice area >20mm^2), NYHA class ≥2, LVEF 15-40%, minimum of one hospitalisation for congestive heart failure within 12 months of randomisation, optimal standard of care therapy for congestive heart failure, not eligible for a mitral surgery intervention according to the heart team
Exclusion criteria	Primary mitral regurgitation, myocardial infarction or coronary artery bypass grafting within 3 months prior to randomisation, cardiac resynchronisation therapy within 3 months, need for any cardiovascular surgery, coronary angioplasty within 1 month, previous surgical mitral valve repair, active infection requiring current antibiotic therapy, terminal renal insufficiency (requiring renal replacement therapy), severe hepatic insufficiency, stroke within 3 months, concurrent medical condition with a life expectancy <12 months, uncontrolled systemic hypertension, hypersensitivity to nitinol, participation in another trial, pregnancy, non-fulfillment of echocardiographic inclusion criteria

Recruitment/selection of patients	People recruited from 37 trial centres
Age, gender and ethnicity	Age - Mean (SD): Intervention: 70.1±10.1, Control: 70.6±9.9. Gender (M:F): 227:77. Ethnicity: Not stated
Further population details	1. Age: Mixed (Intervention: 70.1±10.1, Control: 70.6±9.9). 2. Childbearing age: Women not of childbearing age (≥45 years) (Based on mean age being (at it's lowest confidence interval) 60 and greater.). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Inoperable (Those considered suitable for mitral valve surgery by the heart team were excluded). 5. Primary vs secondary valve disease (for MR and TR): Secondary 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=152) Intervention 1: Transcatheter repair. Mitraclip (percutaneous mitral valve repair). Clip delivery system and a steerable guide catheter. Using a femoral approach. Can also use medical therapy. Duration 1 year. Concurrent medication/care: Single implantable cardioverter-defibrillation (48/151), cardiac resynchronisation therapy-defibrillator (46/151), ACE inhibitor/ARB (111/152), angiotensin receptor and neprilysin inhibitors (14/140), beta blockers (134/152), mineralocorticoid receptor antagonist (86/152), loop diuretic (151/152), oral anticoagulants (93/152). Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Not applicable (n=155) Intervention 2: Conservative management - Pharmacological management. Medical therapy alone. Duration 1 year. Concurrent medication/care: Single implantable cardioverter-defibrillation (57/152), cardiac resynchronisation therapy-defibrillator (35/152), ACE inhibitor/ARB (113/152), angiotensin receptor and neprilysin inhibitors (17/140), beta blockers (138/152), mineralocorticoid receptor antagonist (80/151), loop diuretic (149/152), oral anticoagulants (93/152). Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not applicable
Funding	Study funded by industry (Abbott Vascular)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus PHARMACOLOGICAL MANAGEMENT

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral regurgitation: Death from any cause at 2 year; Group 1: Observed events 53 n=152 ; Group 2: Observed events 52 n=152; HR 1.02; Lower CI 0.7 to Upper CI 1.5; Actuarial or Kaplan Meier curves reported? Kaplan Meier curve reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 152 allocated. Some switching present but analysed ITT. Reason missing unclear.; Group 2 Number missing: 15, Reason: 155 allocated. 3 lost due to consent issues. Some switching present but analysed ITT. Reason for others missing unclear.
- Actual outcome for Mitral regurgitation: Death from any cause at 2 year; Group 1: 53/152, Group 2: 52/152
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 152 allocated. Some switching present but analysed ITT. Reason missing unclear.; Group 2 Number missing: 15, Reason: 155 allocated. 3 lost due to consent issues. Some switching present but analysed ITT. Reason others missing unclear.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral regurgitation: Cardiovascular death at 2 year; Group 1: Observed events 47 n=152 ; Group 2: Observed events 48 n=152; HR 0.99; Lower CI 0.66 to Upper CI 1.48; Actuarial or Kaplan Meier curves reported? Kaplan Meier curve reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 152 allocated. Some switching but analysed ITT. Reason missing unclear.; Group 2 Number missing: 15, Reason: 155 allocated. 3 lost due to consent issues. Some switching but analysed ITT. Reason others missing unclear
- Actual outcome for Mitral regurgitation: Cardiovascular death at 2 year; Group 1: 47/152, Group 2: 48/152
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 152 allocated. Some switching but analysed ITT. Reason missing unclear; Group 2 Number missing: 15, Reason: 155 allocated. 3 lost due to consent issues. Some switching but analysed ITT. Reason others missing unclear

Protocol outcome 3: Interevention-related mortality at 30 days
- Actual outcome for Mitral regurgitation: Death from any cause at 30 days; Group 1: 5/152, Group 2: 4/152
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: 152 allocated. Some switching present but analysed ITT.; Group 2

Number missing: 3, Reason: 155 allocated. 3 lost due to consent issues. Some switching present but analysed ITT.

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Mitral regurgitation: Quality of life at 1 year; Group 1: mean 60.8 (SD 20.3); n=93, Group 2: mean 58.6 (SD 18.2); n=87; EQ-5D 0-100 Top=High is good outcome; Comments: Baseline value intervention: 51.5±19.2 (measured in 143 patients); Baseline value control: 53.2±16.6 (measured in 128 patients)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 59, Reason: 152 allocated. Reason missing unclear for all - potentially issues with completion of the questionnaire.; Group 2 Number missing: 68, Reason: 152 allocated. 3 lost to consent issues. Reason missing unclear for all others - potentially issues with completion of the questionnaire.

Protocol outcome 5: Onset or exacerbation of heart failure at ≥12 months
- Actual outcome for Mitral regurgitation: Hospitalisation for congestive heart failure at 2 year; Group 1: Observed events 85 n=152 ; Group 2: Observed events 94 n=152; HR 0.97; Lower CI 0.72 to Upper CI 1.3; Actuarial or Kaplan Meier curves reported? Kaplan Meier curve reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 152 allocated. Some switching but analysed ITT. Reason missing unclear.; Group 2 Number missing: 15, Reason: 155 allocated. 3 lost due to consent issues. Some switching but analysed ITT. Reason others missing unclear.
- Actual outcome for Mitral regurgitation: Hospitalisation for congestive heart failure at 2 year; Group 1: 85/152, Group 2: 94/152
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 152 allocated. Some switching present but analysed ITT. Reason missing unclear; Group 2 Number missing: 15, Reason: 155 allocated. 3 lost due to consent issues. Some switching present but analysed ITT. Reason others missing unclear

Protocol outcome 6: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral regurgitation: Cardiac embolism (gas embolism or stroke) at Periprocedural - no specific time given; Group 1: 2/144, Group 2: 0/152
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Includes gas embolism; Group 1 Number missing: 8, Reason: 152 allocated. 8 missing as did not undergo attempted procedure. Some switching but analysed ITT.; Group 2 Number missing: 3, Reason: 155 allocated. 3 lost due to consent issues. Some switching but analysed ITT.

Protocol outcome 7: Intervention-related major bleeding at 30 days

- Actual outcome for Mitral regurgitation: Severe haemorrhage (BARC type 2 or higher) at Periprocedural - no specific time given; Group 1: 11/152, Group 2: 6/152 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: 152 allocated. Some switching but analysed ITT; Group 2 Number missing: 3, Reason: 155 allocated. 3 lost due to consent issues. Some switching but analysed ITT. Protocol outcome 8: Major vascular complications at 30 days - Actual outcome for Mitral regurgitation: Haemorrhage resulting in transfusion or vascular complication resulting in surgical intervention at Periprocedural - no specific time given; Group 1: 5/144, Group 2: 0/152 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8, Reason: 152 allocated. Data missing from 8 as did not undergo an attempted procedure. Some switching but analysed ITT.; Group 2 Number missing: 3, Reason: 155 allocated. 3 lost due to consent issues.	
Protocol outcomes not reported by the study	Need for re-intervention at ≥12 months; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Renal failure at 30 days

Study	**Popma 2019[299]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1468)
Countries and setting	Conducted in Australia, Canada, France, Japan, Netherlands, New Zealand, USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): Up to 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Aortic stenosis (non-bicuspid)
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic and asymptomatic patients. Symptomatic patients with aortic valve area ≤1.0cm² (or aortic valve area index of ≤0.6cm²/m² or mean gradient ≥40mmHg, or maximal aortic valve velocity ≥4.0m/s by transthoracic echocardiography at rest. For asymptomatic patients very severe aortic stenosis with an aortic valve area of ≤1.0cm² (or aortic valve area index of ≤0.6cm²/m² AND mean gradient ≥60mmHg, OR maximal aortic valve velocity ≥5.0m/s by transthoracic echocardiography at rest, or aortic valve area ≤1.0cm² (or aortic valve area index of ≤0.6cm²/m² and mean gradient ≥40mmHg, or maximal aortic valve velocity ≥4.0m/s by transthoracic echocardiography at rest and exercise tolerance test that demonstrates a limited exercise capacity, abnormal blood pressure response or arrhythmia OR aortic valve area ≤1.0cm² (or aortic valve area index of ≤0.6cm²/m² AND mean gradient ≥40mmHg, or maximal aortic valve velocity ≥4.0m/s by transthoracic echocardiography at rest AND a LVEF <50%. Patient considered low risk for surgery (predicted mortality risk of <3% at 30 days).

Exclusion criteria	Any condition considered a contraindication for bioprosthetic valve placement, known hypersensitivity of contraindication to aspirin, heparin, bivalirudin, ticlopidine and clopidogrel, Nitinol, contrast media, blood dyscrasias, ongoing sepsis (including active endocarditis), any percutaneous coronary or peripheral interventional procedure with a bare metal stent within 30 days prior to randomisation, or drug eluting stent performed within 180 days prior to randomisation, multivessel coronary artery disease with a SYNTAX score >22 and/or unprotected left main coronary artery, symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 10 weeks of assessment, cardiogenic shock, recent CVA or TIA, gastrointestinal bleeding, patient refuses a blood transfusion, severe dementia, estimated life expectancy of less than 24 months due to associated non-cardiac co-morbid conditions, other medical, social or psychological conditions that in the opinion of the investigator precludes the patient from appropriate consent or adherence to the protocol required follow-up exams, current participating in an investigational drug or another device trial, evidence of acute MI <30 days before the trial procedure due to unstable coronary artery disease, need for emergency surgery of any reason, patient is pregnant or breast feeding, patient is less than the legal age of consent, legally incompetent or otherwise vulnerable, pre-existing prosthetic heart valve in any position, severe mitral regurgitation amenable to surgical replacement or repair, severe tricuspid regurgitation amenable to surgical replacement or repair, moderate or severe mitral stenosis amenable to surgical replacement or repair, hypertrophic obstructive cardiomyopathy with left ventricular outflow gradient, bicuspid aortic valve verified by echocardiography, multidetector computed tomography or magnetic resonance imaging, prohibitive left ventricular outflow tract calcification, sinus of Valsalva diameter unsuitable for placement of the self-expanding bioprosthesis, aortic annulus diameter of <18 or >30mm, significant aortopathy requiring ascending aortic replacement, access vessel mean diameter <5.0mm for Evolut 23R, 26R, or 29R mm transcatheter aortic valves or access vessel mean diameter <5.5mm for Evolut 34R mm or Evolut PRO transcatheter aortic valves. However, for transaxillary (subclavian) access in patients with a patent left internal mammary artery graft access vessel mean diameter <5.5mm for Evolut 23R, 26R, 29R mm transcatheter aortic valves, or access vessel mean diameter <6.0mm for the CoreValve 31mm, Evolut R 34R or Evolut PRO transcatheter aortic valves.
Recruitment/selection of patients	Nothing additional stated
Age, gender and ethnicity	Age - Mean (SD): TAVR: 74.0±5.9, SAVR: 73.8±6.0. Gender (M:F): 956:512. Ethnicity: Not stated

Further population details	1. Age: <75 years (Mean age in both groups <75 years). 2. Childbearing age: Not stated / Unclear (No patients were pregnant or breastfeeding, but not explicitly stated). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Low (Stated in paper. STS-PROM TAVR: 1.9±0.7, STS-PROM SAVR: 1.9±0.7). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=734) Intervention 1: Transcatheter replacement with biological valves. With one of three valve brands: CoreValve, Evolut R, or Evolut PRO. Majority (99%) iliofemoral access. Duration N/A - surgical procedure. Concurrent medication/care: Recommended to have 30 days or more of dual antiplatelet therapy followed by aspirin for 12 months. Pre-TAVR balloon valvuloplasty in 34.9% of patients. Post-TAVR balloon dilation in 31.3% of patients. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Transfemoral 2. Valve type: Biological (n=734) Intervention 2: Surgical replacement with biological or mechanical valve (unclear/mixed invasiveness). Surgeon choice on valve, but no mechanical valves. Unclear if minimally invasive or standard surgery. Duration N/A - surgical procedure. Concurrent medication/care: Recommended that patients are started on warfarin or aspirin after the procedure. Concomitant procedures included aortic root enlargement (1.6%), CABG (13.6%), surgical treatment of atrial fibrillation (3.5%), left atrial appendage closure (6.2%), patent foramen ovale closure (0.7%), mitral valve repair (0.6%), other (5.0). Indirectness: Serious indirectness; Indirectness comment: Unclear invasiveness of surgery Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological
Funding	Study funded by industry (Supported by Medtronic)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPLACEMENT WITH BIOLOGICAL VALVES versus SURGICAL REPLACEMENT WITH BIOLOGICAL VALVES (UNCLEAR/MIXED INVASIVENESS)

Protocol outcome 1: All-cause mortality at ≥12 months

- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 24 months; Group 1: 33/734, Group 2: 33/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - As-treated (those in original, randomised groups that had an attempted procedure) analysis with imputation for those with no data for 24 month follow-up. ITT with imputation as reported in the study.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 662, Reason: 725 patients received the procedure. 24 month follow up was available for 72 patients. However, they used Bayesian analysis to estimate the results in the remainder of the population.; Group 2 Number missing: 669, Reason: 678 patients received the procedure. 24 month follow up was available for 65 patients. However, they used Bayesian analysis to estimate the results in the remainder of the population.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Cardiovascular death at 12 months; Group 1: 13/734, Group 2: 19/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ITT (those in original, randomised groups regardless of which procedure they had if any) analysis with possible imputation for those with no data for 12 month follow-up. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 302, Reason: Follow-up at 12 months available for 432 patients. Imputation potentially used for remaining patients randomised but unclear.; Group 2 Number missing: 382, Reason: Follow-up at 12 months available for 352 patients. Imputation potentially used for remaining patients randomised but unclear.

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 30 days; Group 1: 4/734, Group 2: 10/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ITT (those in original, randomised groups regardless of which procedure they had if any) analysis with possible imputation for those with no data for 30 day follow-up. Level of missing data unclear. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness; Group 1 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point; Group 2 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Mean KCCQ score at 12 months; Group 1: mean 90.3 (SD 12.7); n=429, Group 2: mean 90.8 (SD 12.4); n=349; KCCQ 0-100 Top=High is good outcome; Comments: Uses the as-treated population. Baseline values: TAVR, 68.7 (21.8, n=722); surgery,

69.3 (20.7, n=674)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ITT (those in original, randomised groups regardless of which procedure they had if any) analysis with possible imputation for those with no data for 30 day follow-up. Level of missing data unclear. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 302, Reason: At this prespecified interim analysis, 12-month follow-up was available for 432 patients in the TAVR group and 352 in the
surgery group; Group 2 Number missing: 382, Reason: At this prespecified interim analysis, 12-month
follow-up was available for 432 patients in the TAVR group and 352 in the
surgery group

Protocol outcome 5: Onset or exacerbation of heart failure at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Heart failure rehospitalisation at 12 months; Group 1: 24/734, Group 2: 48/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ITT (those in original, randomised groups regardless of which procedure they had if any) analysis with possible imputation for those with no data for 12 month follow-up. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: Serious indirectness, Comments: Others may have experienced onset/worsening of heart failure without needing hospitalisation for it. Therefore outcome used may not capture all events we would be interested in; Blinding details: Committee adjudicated all end-points and unclear if blinded to the intervention for this outcome; Group 1 Number missing: 302, Reason: Follow-up at 12 months available for 432 patients. Imputation potentially used for remaining patients randomised but unclear.; Group 2 Number missing: 382, Reason: Follow-up at 12 months available for 352 patients. Imputation potentially used for remaining patients randomised but unclear.

Protocol outcome 6: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): All stroke (disabling and non-disabling) at 30 days; Group 1: 25/734, Group 2: 25/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ITT (those in original, randomised groups regardless of which procedure they had if any) analysis with possible imputation for those with no data for 30 day follow-up. Level of missing data unclear. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness; Blinding details: Committee adjudicated all end-points and unclear if blinded to intervention for this outcome; Group 1 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point; Group 2 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point
- Actual outcome for Aortic stenosis (non-bicuspid): TIA at 30 days; Group 1: 4/734, Group 2: 4/734; Comments: Analysed by Bayesian analysis. Number

of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ITT (those in original, randomised groups regardless of which procedure they had if any) analysis with possible imputation for those with no data for 30 day follow-up. Level of missing data unclear. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness; Blinding details: Committee adjudicated all end-points and unclear if blinded to intervention for this outcome; Group 1 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point; Group 2 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point

Protocol outcome 7: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Life-threatening or disabling bleeding at 30 days; Group 1: 18/734, Group 2: 55/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - As-treated (those in original, randomised groups that had an attempted procedure) analysis with possible imputation for those with no data for 30 day follow-up. Level of missing data unclear. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness; Blinding details: Committee adjudicated all end-points and unclear if blinded to intervention for this outcome; Group 1 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point; Group 2 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point

Protocol outcome 8: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Aortic reintervention at 12 months; Group 1: 5/734, Group 2: 4/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ITT (those in original, randomised groups regardless of which procedure they had if any) analysis with possible imputation for those with no data for 12 month follow-up. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness; Group 1 Number missing: 302, Reason: Follow-up at 12 months available for 432 patients. Imputation potentially used for remaining patients randomised but unclear.; Group 2 Number missing: 382, Reason: Follow-up at 12 months available for 352 patients. Imputation potentially used for remaining patients randomised but unclear.

Protocol outcome 9: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Permanent pacemaker implantation at 30 days; Group 1: 128/734, Group 2: 45/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low,

Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - As-treated (those in original, randomised groups that had an attempted procedure) analysis with possible imputation for those with no data for 30 day follow-up. Level of missing data unclear. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness; Group 1 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point; Group 2 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point

Protocol outcome 10: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New atrial fibrillation at 30 days; Group 1: 57/734, Group 2: 260/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - As-treated (those in original, randomised groups that had an attempted procedure) analysis with possible imputation for those with no data for 30 day follow-up. Level of missing data unclear. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness; Blinding details: Committee adjudicated all end-points and unclear if blinded to intervention for this outcome; Group 1 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point; Group 2 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point

Protocol outcome 11: Prosthetic valve endocarditis at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Prosthetic valve endocarditis at 12 months; Group 1: 2/734, Group 2: 3/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ITT (those in original, randomised groups regardless of which procedure they had if any) analysis with possible imputation for those with no data for 12 month follow-up. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness ; Blinding details: Committee adjudicated all end-points and unclear if blinded to intervention for this outcome; Group 1 Number missing: 302, Reason: Follow-up at 12 months available for 432 patients. Imputation potentially used for remaining patients randomised but unclear.; Group 2 Number missing: 382, Reason: Follow-up at 12 months available for 352 patients. Imputation potentially used for remaining patients randomised but unclear.

Protocol outcome 12: Major vascular complications at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major vascular complications at 30 days; Group 1: 28/734, Group 2: 24/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - As-treated (those in original, randomised groups that had an attempted procedure) analysis

with possible imputation for those with no data for 30 day follow-up. Level of missing data unclear. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness ; Blinding details: Committee adjudicated all end-points and unclear if blinded to intervention for this outcome; Group 1 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point; Group 2 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point Protocol outcome 13: Renal failure at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): AKI stage 2/3 at 30 days; Group 1: 7/734, Group 2: 21/734; Comments: Analysed by Bayesian analysis. Number of events estimated from median percentages. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - As-treated (those in original, randomised groups that had an attempted procedure) analysis with possible imputation for those with no data for 30 day follow-up. Level of missing data unclear. Potentially used imputation but unclear for this time-point.; Indirectness of outcome: No indirectness ; Blinding details: Committee adjudicated all end-points and unclear if blinded to intervention for this outcome; Group 1 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point; Group 2 Number missing: , Reason: Proportion with missing data that may have been imputed unclear at this time-point	
Protocol outcomes not reported by the study	Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months

Study	Reyes 1994[314]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in India; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: History taking, echocardiography, exercise testing and chest radiography
Stratum	Mitral stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	People age 15 to 75 years with severe rheumatic mitral stenosis and no history of other cardiac disease or stroke, who were in sinus rhythm, and had no severe subvalvular disease, calcification or more than mild mitral regurgitation.
Exclusion criteria	Coexisting myocardial or other valvular disease, noncritical mitral stenosis, severe pulmonary hypertension, low body weight, severe subvalvular disease, Lutembacher's syndrome, refusal to undergo randomisation and left atrial thrombus demonstrated via echocardiography.
Recruitment/selection of patients	Patients were recruited during a three-week period in August and September 1989.
Age, gender and ethnicity	Age - Mean (SD): Balloon valvuloplasty: 30±9, Surgery: 31±9. Gender (M:F): 47:13. Ethnicity: Not stated

Further population details	1. Age: <75 years (Mean age balloon valvuloplasty: 30±9, Surgery: 31±9). 2. Childbearing age: Women of childbearing age (<45) 3. Morphology (for MS): Not stated / Unclear 4. Operative risk (for AS and MR): Not applicable 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	Serious indirectness: Includes patients aged 15 and over, with at least one patient aged 15 in each arm of the study (age range = 15-50, study protocol included patients aged 15 to 75).
Interventions	(n=30) Intervention 1: Transcatheter repair. Percutaneous balloon valvuloplasty. Duration N/A - surgical procedure. Concurrent medication/care: No background/additional treatment noted. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Not stated / Unclear (n=30) Intervention 2: Standard surgery repair - Standard surgery - repair. Conventional surgical repair - open surgical commissurotomy via midline sternotomy. Duration N/A - surgical procedure. Concurrent medication/care: No background/additional treatment stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear
Funding	Academic or government funding (Funding from Nizam's Institute of Medical Sciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus STANDARD SURGERY - REPAIR

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral stenosis: Death at 3 years; Group 1: 1/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex is different between the groups (balloon valvuloplasty = 2/28 (M/F) while surgery = 11/19) and exercise duration was significantly higher in the surgery group (balloon valvuloplasty = 3.7+/-2.1, surgery = 5.2+/-2.9).; Group 1 Number missing: 0; Group 2 Number missing: 0

	Protocol outcome 2: Cardiac mortality at ≥12 months - Actual outcome for Mitral stenosis: Death from cardiovascular causes at 3 years; Group 1: 1/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex is different between the groups (balloon valvuloplasty = 2/28 (M/F) while surgery = 11/19) and exercise duration was significantly higher in the surgery group (balloon valvuloplasty = 3.7+/-2.1, surgery = 5.2+/-2.9).; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Intervention-related mortality at 30 days - Actual outcome for Mitral stenosis: Early death at 30 days (postoperatively); Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex is different between the groups (balloon valvuloplasty = 2/28 (M/F) while surgery = 11/19) and exercise duration was significantly higher in the surgery group (balloon valvuloplasty = 3.7+/-2.1, surgery = 5.2+/-2.9).; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Intervention-related stroke or TIA at 30 days - Actual outcome for Mitral stenosis: Stroke at 30 days (postoperatively); Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex is different between the groups (balloon valvuloplasty = 2/28 (M/F) while surgery = 11/19) and exercise duration was significantly higher in the surgery group (balloon valvuloplasty = 3.7+/-2.1, surgery = 5.2+/-2.9).; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Intervention-related atrial fibrillation at 30 days - Actual outcome for Mitral stenosis: Atrial fibrillation at 30 days (postoperatively); Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex is different between the groups (balloon valvuloplasty = 2/28 (M/F) while surgery = 11/19) and exercise duration was significantly higher in the surgery group (balloon valvuloplasty = 3.7+/-2.1, surgery = 5.2+/-2.9).; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related major bleeding at 30 days; Need for re-intervention at ≥12 months; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days;

Prosthetic valve endocarditis at ≥12 months	Major vascular complications at 30 days; Renal failure at 30 days

Study	Rifaie 2009[322]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Egypt; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): Mean: 8.25±1 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Mitral stenosis: Moderate to severe mitral stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Moderate to severe mitral stenosis suffering from pulmonary congestion symptoms
Exclusion criteria	Mitral regurgitation grade >2/4; more than minimal or mild mitral valve calcification by echocardiography; previous surgical commissurotomy; those with thrombi in left atrial cavity; history of prior systemic embolisation; concomitant valve disease requiring surgical intervention; those indicated for coronary artery bypass surgery; those with limited life expectancy due to coexistent disease (e.g. malignancy)
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 29.7±7. Gender (M:F): 12/28. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mean age: 29.7±7). 2. Childbearing age: Women of childbearing age (<45) (Mean age <45 years). 3. Morphology (for MS): Morphology suitable for transcatheter intervention 4. Operative risk (for AS

	and MR): Not applicable 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Transcatheter repair. Percutaneous mitral valvotomy - performed through standard double balloon technique. Duration N/A (surgical procedure). Concurrent medication/care: Patients in atrial fibrillation received oral anticoagulants for 6 weeks prior aiming for an INR=2-3. Stopped before the procedure so INR decreased below 1.5. Otherwise not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Not applicable (n=20) Intervention 2: Minimally invasive surgery repair. Left thoracotomy with a Tubb's dilator (opened to a maximum of 2.5cm in women and 3.5cm in men). Duration N/A (surgical intervention). Concurrent medication/care: Patients in atrial fibrillation received oral anticoagulants for 6 weeks prior aiming for an INR=2-3. Stopped before the procedure so INR decreased below 1.5. Otherwise not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus MINIMALLY INVASIVE SURGERY REPAIR

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral stenosis: Mortality at 8 years; Group 1: 0/19, Group 2: 0/18
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 20 randomised. 2 switched over to the surgical arm due to severe subvalvular fibrosis (however, analysed in their intended group). 1 dropped out after the 30 day follow up period.; Group 2 Number missing: 2, Reason: 20 randomised. 2 dropped out after the 30 day follow up period.

Protocol outcome 2: Cardiac mortality at ≥12 months - Actual outcome for Mitral stenosis: Mortality at 8 years; Group 1: 0/19, Group 2: 0/18 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 20 randomised. 2 switched over to the surgical arm due to severe subvalvular fibrosis (however, analysed in their intended group). 1 dropped out after the 30 day follow up period.; Group 2 Number missing: 2, Reason: 20 randomised. 2 dropped out after the 30 day follow up period. Protocol outcome 3: Intervention-related mortality at 30 days - Actual outcome for Mitral stenosis: Mortality at 30 days; Group 1: 0/20, Group 2: 0/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 20 randomised. 2 switched over to the surgical arm due to severe subvalvular fibrosis (however, analysed in their intended group).; Group 2 Number missing: 0, Reason: 20 randomised. Protocol outcome 4: Intervention-related stroke or TIA at 30 days - Actual outcome for Mitral stenosis: Hemiplegia at 30 days; Group 1: 1/20, Group 2: 0/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Might not be referring to stroke/TIA; Group 1 Number missing: 0, Reason: 20 randomised. 2 switched over to the surgical arm due to severe subvalvular fibrosis (however, analysed in their intended group).; Group 2 Number missing: 0, Reason: 20 randomised. Protocol outcome 5: Need for re-intervention at ≥12 months - Actual outcome for Mitral stenosis: Reoperation at 8 years; Group 1: 4/19, Group 2: 0/18; Comments: Transcatheter repair: n=2 had suboptimal repair following PMV so crossed over to surgical group at time of procedure; n=2 had repeat transcatheter procedure due to restenosis during follow-up Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 20 randomised. 2 switched over to the surgical arm due to severe subvalvular fibrosis (however, analysed in their intended group). 1 dropped out after the 30 day follow up period.; Group 2 Number missing: 2, Reason: 20 randomised. 2 dropped out after the 30 day follow up period.	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related major bleeding at 30 days; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days;

Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days	

Study (subsidiary papers)	QUALITY-AVR trial: Rodriguez-caulo 2020[324] (Rodriguez-caulo 2018[325])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Spain; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention and 12 month follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Not well described, but mentions measurements likely to have been performed on echocardiography
Stratum	Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Severe aortic stenosis, unclear whether bicuspid excluded
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥18 years; required isolated surgical aortic valve replacement according to guidelines due to symptomatic (dyspnoea NYHA score ≥2, angina or syncope) severe aortic stenosis (calcified aortic valve, aortic valve area <1 cm^2 or body surface area index <0.6 cm^2, mean transvalvular gradient >40 mmHg or peak systolic velocity >4 m/s) or double aortic lesion with predominant stenosis; and ability to provide informed consent
Exclusion criteria	Moderately depressed ejection fraction (<40%); prior heart surgery (redo operation); emergent surgery (within first 24 h of admission); infectious endocarditis; more than moderate chronic obstructive pulmonary disease (forced expiratory volume at 1 second predicted <60% measured by spirometry); and need for concomitant surgery (except Morrow myectomy) preoperatively or intraoperatively
Recruitment/selection of patients	Unclear if consecutive

Age, gender and ethnicity	Age - Mean (SD): Ministernotomy, 66.2 (11.2) years; full sternotomy, 67.6 (7.5) years. Gender (M:F): Ministernotomy, 27/23; full sternotomy, 30/20. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean age <75 years in both groups). 2. Childbearing age: Women not of childbearing age (≥45 years) (Not limited to women, but mean age is 66-67 in both groups). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear (Operative risk not reported, though logistic EuroSCORE of 4-5 reported - likely low risk?). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Extra comments	. EuroSCORE logistic 1, mean (SD): 5.2 (4.2) vs. 4.3 (2.1)%; hypertension, 78% vs. 84%; diabetes, 34% vs. 30%; hypercholesterolaemia, 64% vs. 62%; previous stroke, 10% vs. 4%; peripheral artery disease, 6% vs. 4%; COPD, 34% vs. 26%; previous myocardial infarction, 6% vs. 10%; pulmonary hypertension, 8% vs. 12%; chronic kidney disease, 10% vs. 24%; creatinine, mean (SD): 1.0 (0.3) vs. 1.0 (0.3) mg/dl; ejection fraction, mean (SD): 64.2 (6.9) vs. 66.4 (8.1)%; atrial fibrillation, 12% vs. 12%; body mass index, mean (SD): 28.5 (4.8) vs. 28.7 (4.8) kg/m²; haemoglobin, mean (SD): 13.2 (1.6) vs. 13.3 (1.7) mg/dl; mean aortic gradient, mean (SD): 53.6 (12.4) vs. 53.3 (11.5) mmHg; NYHA class, mean (SD): 2.4 (0.5) vs. 2.3 (0.6).
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Ministernotomy replacement with biological or mechanical valve. Ministernotomy aortic valve replacement. Partial upper hemisternotomy extended into a J-shape into the right fourth intercostal space irrespective of the skin incision (usually 10 cm in length). All surgeons were experienced in ministernotomy. Procedure was completed in 94%, with 3 being converted to full sternotomy due to difficulties with the procedure. 49 (98%) received a bioprosthesis. Duration NA - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological (98% received a bioprosthesis). (n=50) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Full sternotomy aortic valve replacement. Conventional median sternotomy performed from the manubrium to the xiphoid, with conventional cardiopulmonary bypass.

	48 (96%) had a bioprosthesis. Duration NA - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological (96% received a bioprosthesis).
Funding	Academic or government funding (Supported by grants from Spanish Cardiovascular Research Network co-founded by FEDER.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE (MAJORITY BIOLOGICAL) versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES (MAJORITY BIOLOGICAL)

Protocol outcome 1: Interevention-related mortality at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): All-cause mortality at 30 days; Group 1: 1/50, Group 2: 2/50; Comments: Causes of death were bronchoaspiration pnuemonia, acute respiratory distress syndrome with cardiogenic shock and one death was due to an unknown cause. All were at intermediate risk (logistic Euroscore 1 >10%)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Quality of life at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): EQ-5D-5L index at 12 months; Group 1: mean 0.92 (SD 0.09); n=47, Group 2: mean 0.9 (SD 0.16); n=47; EQ-5D-5L -0.654 - 1.00 Top=High is good outcome; Comments: Standard deviations reported in supplementary material. Baseline values: ministernotomy, 0.67 (0.21); full sternotomy, 0.75 (0.09). P=0.015.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: patients said to be blinded but difficult to ensure given scar sizes may differ. ; Indirectness of outcome: No indirectness; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. Also a difference in this measure at baseline (0.67 vs. 0.75); Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): EQ-5D-5L utilities - health index at 12 months; Group 1: mean 94.5 (SD 6.8); n=47, Group 2: mean 92.9 (SD 11.7); n=47; EQ-5D-5L utilities - health index 0-100 Top=High is good outcome; Comments: Reported in supplementary materials. Baseline values: ministernotomy, 75.4 (4.0); full sternotomy, 80.2 (0.1). P=0.19.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: patients said to be blinded but difficult to ensure given scar sizes may differ. ; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. Also a difference in this measure at baseline (75.4 vs. 80.2); Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): EQ-5D-5L utilities - severity index at 12 months; Group 1: mean 5.4 (SD 6.8); n=47, Group 2: mean 7.1 (SD 11.7); n=47; EQ-5D-5L utilities - severity index 0-100 Top=High is poor outcome; Comments: Reported In supplementary materials. Baseline values: ministernotomy, 25.6 (14.0); full sternotomy, 19.8 (10.0). P=0.019.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: patients said to be blinded but difficult to ensure given scar sizes may differ. ; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. Also a difference in this measure at baseline (25.6 vs. 19.8); Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): EQ-5D-5L utilities - visual scale at 12 months; Group 1: mean 79.35 (SD 16.35); n=47, Group 2: mean 80.43 (SD 15.63); n=47; EQ-5D-5L utilities - visual scale 0-100 Top=High is good outcome; Comments: Reported in supplementary material. Baseline values: ministernotomy, 54.30 (15.52); full sternotomy, 59.40 (13.31). P=0.081.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: patients said to be blinded but difficult to ensure given scar sizes may differ. ; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. Also a difference in this measure at baseline (54.30 vs. 59.40); Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear

Protocol outcome 3: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Stroke at 30 days; Group 1: 1/50, Group 2: 1/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Transfusions at 72 h; Group 1: 22/50, Group 2: 25/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Unclear if all events were due to bleeding events ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Reintervention at 30 days; Group 1: 3/50, Group 2: 2/50

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: 30 day reporting only; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Length of hospital stay at after intervention
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Intensive care unit stay at In-hospital; Group 1: mean 3.65 Days (SD 3.01); n=50, Group 2: mean 5.06 Days (SD 6.85); n=50
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: knowledge of operation received may have affected length of stay?; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Total hospital stay at In-hospital; Group 1: mean 8.38 (SD 4.06); n=50, Group 2: mean 10.33 (SD 10.36); n=50
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: knowledge of operation received may have affected length of stay?; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Permanent pacemaker at Unclear; Group 1: 0/50, Group 2: 3/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 8: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Postoperative atrial fibrillation at Postoperative; Group 1: 13/50, Group 2: 17/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 9: Prosthetic valve endocarditis at ≥12 months
- Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Early endocarditis at 12 months; Group 1: 1/47, Group 2: 1/47

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. Also a difference in this measure at baseline (0.67 vs. 0.75); Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear Protocol outcome 10: Renal failure at 30 days - Actual outcome for Aortic stenosis (mixed bicuspid and non-bicuspid or unclear): Acute kidney injury 2-3 at 30 days; Group 1: 3/50, Group 2: 9/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline larger than others (proportion with chronic kidney disease. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Re-hospitalisation at ≥12 months; Major vascular complications at 30 days

Study	Shneider 2020[347]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=112)
Countries and setting	Conducted in Russia; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Mean follow-up was 32-34 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Indications for intervention determined through guidelines for management of aortic valve diseases
Stratum	Mixed/unclear aortic valve disease: Those with indications for isolated aortic valve replacement (unclear proportion with stenosis and/or regurgitation)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-85 years; indications for isolated aortic valve replacement
Exclusion criteria	Not reported
Recruitment/selection of patients	Unclear if consecutive
Age, gender and ethnicity	Age - Mean (SD): Partial upper sternotomy, 53.1 (14.9) years; midline sternotomy, 56.1 (14.3) years. Gender (M:F): Partial upper sternotomy, 24/32; midline sternotomy, 25/31. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean age in both groups <75 years). 2. Childbearing age: Women not of childbearing age (≥45 years) (Group not limited to women, but mean age in both groups >45 years). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear (Unclear if all had aortic stenosis, but

	EuroSCORE II ~2 in each group). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not stated / Unclear (Unclear if all had AR, but LVEF ~58% for both groups).
Extra comments	Body mass index, mean (SD): 30.2 (5.7) vs. 30.5 (5.1) kg/m²; EuroSCORE II, mean (SD): 2.3 (0.7)% vs. 2.6 (0.5)%; NYHA class I (0% vs. 0%), II (21.4% vs. 30.4%), III (73.2% vs. 60.7%) and IV (5.4% vs. 3.6%); peak pressure gradient, mean (SD): 102.8 (25.3) vs. 106.2 (23.9) mmHg; LV end-diastolic volume, mean (SD): 89.3 (31.7) vs. 80.2 (24.4) ml; LV ejection fraction, mean (SD): 58.3 (5.6) vs. 58.5 (5.1)%; interventricular septum thickness, mean (SD): 1.8 (0.4) vs. 1.9 (0.3) mm; chronic obstructive pulmonary disease, 26.8% vs. 10.7%; chronic kidney disease, 10.7% vs. 7.1%; diabetes mellitus, 17.8% vs. 21.4%.
Indirectness of population	Serious indirectness: Mixed/unclear population of aortic valve disease (unclear proportion with stenosis and/or regurgitation as indication for surgery)
Interventions	(n=56) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves. J-shaped partial upper sternotomy. 75% received On-X mechanical prosthesis and 25% received Edwards Perimount stented bioprosthesis. Preoperative chest CT performed in all patients for navigation and analysis of possibility of J-shaped procedure and to reduce the risk of conversion. Incision made up to the 3rd or 4th intercostal space depending on CT data. . Duration NA - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (75% mechanical). (n=56) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Midline sternotomy. 69.6% received On-X mechanical prosthesis and 30.4% received Edwards Perimount stented bioprosthesis. Preoperative chest CT performed in all patients for navigation and analysis of possibility of J-shaped procedure and to reduce the risk of conversion. Incision made up to the 3rd or 4th intercostal space depending on CT data. . Duration NA - surgical procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (70% mechanical).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINIMALLY INVASIVE SURGERY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES (75% MECHANICAL) versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES (70% MECHANICAL)

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: All-cause mortality at 30 months; Group 1: n=56 ; Group 2: n=56; HR 0.57; Lower CI 0.07 to Upper CI 4.4; Test statistic: Not reported; Advantage to research or control? R; Actuarial or Kaplan Meier curves reported? KM curves; Follow up details: KM plot reported up to 30 months; Comments: Number of events not well reported. Hazard ratio estimated using number at risk and KM curve reported in the paper. 30 month KM survival estimate reported to be 93.1% (95% CI 72.7-98.4%) in minimally invasive group and 92.6% (95% CI 78.5-97.6%)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Incomplete outcome: result calculated from KM curves where participants censored when lost to follow-up. Appears to be more lost to follow-up than events recorded; outcome reporting: HR not reported in paper but estimated from curve and number at risk; Indirectness of outcome: No indirectness ; Baseline details: Similar for most of those reported, though some bigger differences (NYHA class and proportion with COPD); Group 1 Number missing: , Reason: Unclear; Group 2 Number missing: , Reason: unclear

Protocol outcome 2: Interevention-related mortality at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: In-hospital mortality at In-hospital; Group 1: 0/56, Group 2: 1/56
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Similar for most of those reported, though some bigger differences (NYHA class and proportion with COPD); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Early postoperative stroke at Postoperative; Group 1: 0/56, Group 2: 3/56
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Similar for most of those reported, though some bigger differences (NYHA class and proportion with COPD); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related major bleeding at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Blood transfusion at Postoperative; Group 1: 3/56, Group 2: 11/56
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Unclear if all transfusions

were due to bleeding events; Baseline details: Similar for most of those reported, though some bigger differences (NYHA class and proportion with COPD); Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Mixed/unclear aortic valve disease: Re-exploration for bleeding at Unclear; Group 1: 2/56, Group 2: 7/56
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Similar for most of those reported, though some bigger differences (NYHA class and proportion with COPD); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Need for re-intervention at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: Redo aortic valve surgery at 30 months; Group 1: n=56 ; Group 2: n=55; HR 0.87; Lower CI 0.17 to Upper CI 4.5; Advantage to research or control? R; Actuarial or Kaplan Meier curves reported? KM; Follow up details: up to 30 months; Comments: Number of events not reported. Hazard ratio estimated using number at risk and KM curve reported in the paper.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Incomplete outcome: result calculated from KM curves where participants censored when lost to follow-up. Appears to be more lost to follow-up than events recorded; outcome reporting: HR not reported in paper but estimated from curve and number at risk; Indirectness of outcome: No indirectness ; Baseline details: Similar for most of those reported, though some bigger differences (NYHA class and proportion with COPD); Group 1 Number missing: , Reason: Unclear; Group 2 Number missing: , Reason: unclear

Protocol outcome 6: Length of hospital stay at after intervention
- Actual outcome for Mixed/unclear aortic valve disease: Intensive care unit stay at In-hospital; Group 1: mean 1.6 Days (SD 0.6); n=56, Group 2: mean 1.7 Days (SD 0.7); n=56
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: knowledge of procedure received may have affected length of stay; Indirectness of outcome: No indirectness ; Baseline details: Similar for most of those reported, though some bigger differences (NYHA class and proportion with COPD); Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Mixed/unclear aortic valve disease: Total hospital stay at In-hospital; Group 1: mean 14.1 Days (SD 5.1); n=56, Group 2: mean 17.9 Days (SD 5.7); n=56
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: knowledge of procedure received may have affected length of stay; Indirectness of outcome: No indirectness ; Baseline details: Similar for most of those reported, though some bigger differences (NYHA class and proportion with COPD); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Permanent pacemaker due to 3rd degree AV block at Operative; Group 1: 0/56, Group 2: 1/56;

Comments: 1 event appears to have occurred operatively. Implanted due to 3rd degree AV block. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Similar for most of those reported, though some bigger differences (NYHA class and proportion with COPD); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Cardiac mortality at ≥12 months; Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Re-hospitalisation at ≥12 months; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study (subsidiary papers)	**Smith 2011[359] (Barbanti 2013[37], Elmariah 2013[113], Généreux 2014[132], Greason 2014[146], Hahn 2013[151], Kodali 2012[199], Lindman 2014[219], Mack 2015[231], Miller 2012[250], Okada 2014[275], Pibarot 2014[295], Reynolds 2012[317], Reynolds 2012[319], Williams 2014[425])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=699)
Countries and setting	Conducted in Canada, Germany, USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiographically defined clear inclusion criteria
Stratum	Aortic stenosis (non-bicuspid)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with severe aortic stenosis (AVA <0.8cm², mean AV gradient ≥40mmHg, or a peak aortic jet velocity of ≥4m/s) and cardiac symptoms (all included were NYHA class II-IV) for whom conventional surgery to replace the aortic valve was associated with high risk (STS score ≥10% or equivalent but not classed as inoperable).
Exclusion criteria	Bicuspid or noncalcified aortic valve, acute MI, substantial coronary artery disease requiring revascularisation, a LVEF <20%, an aortic annulus diameter of <18mm or >25mm, severe (>3+) mitral or aortic regurgitation, a TIA or stroke within the previous 6 months, and severe renal insufficiency, blood dyscrasias, pre-existing prosthetic valve in any position, hypertrophic cardiomyopathy with or without

	obstruction, need for emergency surgery for any reason, active peptic ulcer or upper GI bleeding within the prior 3 months, echocardiographic evidence of an intracardiac mass, thrombus or vegetation, hypersensitivity to aspirin, heparin, ticlopidine or clopidogrel, or sensitivity to contrast media, significant abdominal or thoracic aorta disease, iliofemoral vessel characteristics that would preclude safe placement of a 22F or 24F introducer sheath, currently participating in an investigational drug or another device study, active bacterial endocarditis or other active infections, bulky calcified aortic valve leaflets in close proximity to coronary ostia.
Recruitment/selection of patients	Screened by the investigators and then selected by the executive committee (including people from Edwards Lifesciences)
Age, gender and ethnicity	Age - Mean (SD): TAVR: 83.6±6.8, SAVR: 84.5±6.4. Gender (M:F): 399:300. Ethnicity: Not stated
Further population details	1. Age: 75 years or over (Mean age (including CIs) is greater than 75 years). 2. Childbearing age: Women not of childbearing age (≥45 years) 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): High (STS TAVR: 11.8±3.3, STS SAVR: 11.7±3.5, Logistic EuroSCORE TAVR: 29.3±16.5, Logistic EuroSCORE SAVR: 29.2±15.6). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Extra comments	.
Indirectness of population	Serious indirectness: >10% in each group had received previous balloon aortic valvuloplasty
Interventions	(n=348) Intervention 1: Transcatheter replacement with biological valves. SAPIEN heart valve-system using either transfemoral or transapical placement. Duration N/A - surgical procedure. Concurrent medication/care: Received heparin during the procedure and started on dual antiplatelet therapy (aspirin and clopidogrel) for 6 months afterwards. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not stated / Unclear (Transfemoral in 244, transapical in 104). 2. Valve type: Biological

	(n=351) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. Unclear about type of valves used or pertinent details of the surgical procedure. Duration N/A - surgical procedure. Concurrent medication/care: Received heparin during the procedure and started on dual antiplatelet therapy (aspirin and clopidogrel) for 6 months afterwards. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not stated / Unclear
Funding	Study funded by industry (Funded by Edwards Lifesciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPLACEMENT WITH BIOLOGICAL VALVES versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 5 years; Group 1: Observed events 229 n=348 ; Group 2: Observed events 198 n=351; HR 1.04; Lower CI 0.86 to Upper CI 1.24; Log rank variance: 0.76
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 5 years; Group 1: 229/348, Group 2: 198/351; Comments: Kaplan-Meier estimates used
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Death from cardiovascular causes at 5 years; Group 1: 147/348, Group 2: 123/351; Comments: Determined by Kaplan-Meier estimates

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 30 days; Group 1: 12/348, Group 2: 22/351; Comments: Determined by Kaplan-Meier estimates
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): KCCQ summary score at 12 months; Group 1: mean 28.96 (SD 28.02); n=231, Group 2: mean 25.23 (SD 29.89); n=195; KCCQ summary 0-100 Top=High is good outcome; Comments: Reported as change from baseline so higher positive values indicate better improvements in quality of life compared to baseline. Baseline values: TAVR, 39.6 (21.83, n=328); AVR, 44.47 (21.88, n=300)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Slight difference in outcome measured at baseline; Group 1 Number missing: 117, Reason: Some didn't complete questionnaire at baseline. Reasons for others unclear - likely to include deaths and withdrawals.; Group 2 Number missing: 156, Reason: Some didn't complete questionnaire at baseline. Reasons for others unclear - likely to include deaths and withdrawals.
- Actual outcome for Aortic stenosis (non-bicuspid): SF-12 physical component at 12 months; Group 1: mean 6.539 (SD 11.53); n=221, Group 2: mean 5.598 (SD 11.76); n=185; SF-12 physical component 0-100 Top=High is good outcome; Comments: Reported as change compared with baseline so higher positive value indicates better improvement in quality of life. Baseline values: TAVR, 29.61 (7.613, n=328); AVR, 30.91 (8.229, n=300)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Outcome similar at baseline; Group 1 Number missing: 127, Reason: Some didn't complete questionnaire at baseline. Reasons for others unclear - likely to include deaths and withdrawals.; Group 2 Number missing: 166, Reason: Some didn't complete questionnaire at baseline. Reasons for others unclear - likely to include deaths and withdrawals.
- Actual outcome for Aortic stenosis (non-bicuspid): SF-12 mental component at 12 months; Group 1: mean 4.582 (SD 13); n=221, Group 2: mean 4.449 (SD 12.91); n=185; SF-12 mental component 0-100 Top=High is good outcome; Comments: Reported as change compared with baseline so higher positive value indicates better improvement in quality of life. Baseline values: TAVR, 46.88 (11.47, n=328); AVR, 47.55 (10.65, n=300)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Outcome similar at baseline; Group 1 Number missing: 127, Reason: Some didn't complete questionnaire at baseline. Reasons for others unclear - likely to include deaths and withdrawals.; Group 2 Number missing: 166, Reason: Some didn't complete questionnaire at baseline. Reasons for others unclear - likely to include deaths and withdrawals.
- Actual outcome for Aortic stenosis (non-bicuspid): EQ-5D utilities at 12 months; Group 1: mean 0.082 (SD 0.224); n=221, Group 2: mean 0.07 (SD 0.242); n=183; EQ-5D utilities 0-1 Top=High is good outcome; Comments: Reported as change score compared with baseline so higher positive value indicates better improvement in quality of life. Baseline values: TAVR, 0.663 (0.197, n=328); AVR, 0.677 (0.201, n=300)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Outcome similar at baseline; Group 1 Number missing: 127, Reason: Some didn't complete questionnaire at baseline. Reasons for others unclear - likely to include deaths and withdrawals.; Group 2 Number missing: 166, Reason: Some didn't complete questionnaire at baseline. Reasons for others unclear - likely to include deaths and withdrawals.

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Stroke or TIA at 30 days; Group 1: 19/348, Group 2: 8/351; Comments: Determined by Kaplan-Meier estimates
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.

Protocol outcome 6: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major bleeding at 30 days; Group 1: 32/348, Group 2: 67/351; Comments: KM estimates mentioned
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.

Protocol outcome 7: Length of hospital stay at after intervention
- Actual outcome for Aortic stenosis (non-bicuspid): Median hospital index stay at 30 days; Group 1: mean 8 days (SD 0); n=348, Group 2: mean 12 days (SD 0); n=351; Comments: Is the median score. No confidence intervals given.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier

estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.

Protocol outcome 8: Re-hospitalisation at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Repeat hospital admission at 5 years; Group 1: 108/348, Group 2: 81/351; Comments: Determined by Kaplan-Meier estimates
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.

Protocol outcome 9: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New pacemaker at 30 days; Group 1: 13/348, Group 2: 12/351; Comments: Determined by Kaplan-Meier estimates
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.

Protocol outcome 10: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New-onset atrial fibrillation at 30 days; Group 1: 30/348, Group 2: 56/351; Comments: Determined by Kaplan-Meier estimates
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.

Protocol outcome 11: Prosthetic valve endocarditis at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Endocarditis at 5 years; Group 1: 5/348, Group 2: 6/351; Comments: Determined by Kaplan-Meier estimates
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure. Protocol outcome 12: Major vascular complications at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): Major vascular complications at 30 days; Group 1: 38/348, Group 2: 11/351; Comments: Determined by Kaplan-Meier estimates Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure. Protocol outcome 13: Renal failure at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): Renal-replacement therapy at 30 days; Group 1: 10/348, Group 2: 10/351; Comments: Determined by Kaplan-Meier estimates Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 348 patients assigned. 4 did not receive the procedure. 5 lost to follow up. 4 withdrew after the procedure.; Group 2 Number missing: 0, Reason: Analysed through Kaplan-Meier estimates. 351 patients assigned. 38 did not receive the procedure. 12 lost to follow up. 11 withdrew after the procedure.	
Protocol outcomes not reported by the study	Onset or exacerbation of heart failure at ≥12 months; Need for re-intervention at ≥12 months

Study (subsidiary papers)	**Stone 2018[367] (Arnold 2019[23], Mack 2018[230], Anon 2019[44], Arnold 2020[27], Asch 2019[32])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=614)
Countries and setting	Conducted in Canada, USA; Setting: Unclear - mix of secondary and outpatient?
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Up to 24 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed by echocardiography prior to enrollment
Stratum	Mitral regurgitation
Subgroup analysis within study	Not stratified but pre-specified
Inclusion criteria	Symptomatic secondary MR (3+ or 4+ by independent echocardiographic core laboratory assessment) due to cardiomyopathy of either ischemic or non-ischemic etiology; adequate treatment per applicable standards including for coronrary artery disease, LV dysfunction, mitral regurgitation and heart failure; NYHA functional class II, III or ambulatory IV; at least one hospitalisation for heart failure in 12 months prior to enrollment and/or corrected BNP ≥300 pg/ml or a corrected NT-proBNP ≥1500 pg/ml; local heart team agree mitral valve surgery will not be offered as a treatment option; LVEF ≥20% and ≤50%; LV end-systolic dimension ≤70 mm; primary regurgitant jet is non-commissural and implanting investigator thinks it can be successfully treated by MitraClip; creatine phosphokinase MB isoenzyme obtained within prior 14 days is less than local laboratory upper limit of normal; transseptal catheterisation and femoral vein access is feasible; age 18 years or older; subject or guardian agrees to all provisions of protocol

Exclusion criteria	Untreated clinically significant coronary artery disease requiring revascularisation; CABG, PCI or TAVR within prior 30 days; aortic or tricuspid valve disease requiring surgery or transcatheter intervention; COPD requiring continuous home oxygen therapy or chronic outpatient steroid use; cerebrovascular accident within prior 30 days; severe symptomatic carotid stenosis (>70% by ultrasound); ACC/AHA stage D heart failure; presence of estimated PASP >70 mm unless vasodilator therapy can reduce pulmonary vascular resistance to <3 Wood Units or between 3 and 4.5 Wood Units with v wave less than twice the mean of pulmonary capillary wedge pressure; presence of hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic aetiology; presence of infiltrative cardiomyopathies (e.g. amyloidosis, hemochromatosis, sarcoidosis); haemodynamic instability requiring inotropic support or mechanical heart assistance; physical evidence of right-sided congestive heart failure with echo evidence of moderate or severe right ventricular dysfunction; implant of cardiac resynchronisation therapy (CRT) or CRT-defibrillator within last 30 days; mitral valve orifice area <4 cm^2; leaflet anatomy which may preclude MitraClip implantation, proper positioning on the leaflets or sufficient reduction in MR by the MitraClip; haemodynamic instability defined as systolic pressure <90 mmHg with or without afterload reduction, cardiogenic shock or need for inotropic support or intra-aortic balloon pump or other support device; need for emergent or urgent surgery for any reason or any planned cardiac surgery within next 12 months; life expectancy <12 months due to non-cardiac conditions; Modified Rankin Scale ≥4 disability; status 1 heart transplant or prior orthotopic heart transplantation; prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure; echo evidence of intracardiac mass, thrombus or vegetation; active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease; active infections requiring current antibiotic therapy; transoesophageal echocardiography is contraindicated or high risk; known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically; pregnant or planning pregnancy within next 12 months; currently participating in investigational drug or another device study that has not reached its primary endpoint; belongs to vulnerable population or has any disorder that compromises ability to provide written informed consent and/or to comply with study procedures
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Transcatheter valve repair + medical, 71.7 (11.8) years; medical only, 72.8 (10.5) years. Gender (M:F): Transcatheter valve repair + medical, 201/101; medical only, 192/120. Ethnicity: Not reported

Further population details	1. Age: <75 years (Mean age in both groups <75 years). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Inoperable (To be included, cardiothoraric surgeon had to consider mitral valve surgery inappropriate). 5. Primary vs secondary valve disease (for MR and TR): Secondary (All had secondary MR). 6. Systolic dysfunction (for AR): Not applicable
Extra comments	. Diabetes, 35.1 vs. 39.4%; hypertension, 66.6 vs. 61.5%; hypercholesterolaemia, 55.0 vs. 52.2%; previous myocardial infarction, 51.7 vs. 51.3%; previous percutaneous coronary intervention, 43.0 vs. 49.0%; previous coronary artery bypass grafting, 40.1 vs. 40.4%; previous stroke or TIA, 18.5 vs. 15.7%; peripheral vascular disease, 17.2 vs. 18.3%; chronic obstructive pulmonary disease, 23.5 vs. 23.1%; history of atrial fibrillation or flutter, 57.3 vs. 53.2%; mean (SD) BMI, 27.0 (5.8) vs. 27.1 (5.9); creatinine clearance ≤60 ml/min, 71.6 vs. 75.2%; anaemia, 59.8 vs. 62.7%; STS risk score ≥8%, 41.7 vs. 43.6%; high risk of surgery-related complications or death, 68.6 vs. 69.9%; ischemic cause of cardiomyopathy, 60.9 vs. 60.6%; non-ischemic cause of cardiomyopathy, 39.1 vs. 39.4%; NYHA class I (0.3 vs. 0%), II (42.7 vs. 35.4%), III (51.0 vs. 54.0%) and IVa ambulatory (6.0 vs. 10.6%); heart failure hospitalisation within previous 12 months, 58.3 vs. 56.1%; previous cardiac resynchronisation therapy, 38.1 vs. 34.9%; previous implantation of defibrillator, 30.1 vs. 32.4%; mean (SD) BNP level, 1014.8 (1086) vs. 1017.1 (1212.8) pg/ml; mean (SD) NT-proBNP level, 5174.3 (6566.6) vs. 5943 (8437.6) pg/ml; moderate to severe (3+) mitral regurgitation, 49.0 vs. 55.3%; severe (4+) mitral regurgitation, 51.0 vs. 44.7%; mean (SD) effective regurgitant orifice area, 0.41 (0.15) vs. 0.40 (0.15) cm^2; mean (SD) LV end-systolic dimension, 5.3 (0.9) vs. 5.3 (0.9) cm; mean (SD) LV end-diastolic dimension, 6.2 (0.7) vs. 6.2 (0.8) cm; mean (SD) LV end-systolic volume, 135.5 (56.1) vs. 134.3 (60.3) ml; mean (SD) LV end-diastolic volume, 194.4 (69.2) vs. 191.0 (72.9) ml; LVEF ≤40%, 82.2 vs. 82.0%; mean (SD) right ventricular systolic pressure, 44.0 (13.4) vs. 44.6 (14.0) mmHg
Indirectness of population	No indirectness
Interventions	(n=302) Intervention 1: Transcatheter repair. Transcatheter mitral valve repair with the MitraClip device and guideline-directed medical therapy. Repair performed under conscious sedation of general anaesthesia. Femoral venous access obtained and inter-atrial septum crossed using standard techniques. If placement of one MitraClip device does not lead to sufficient reduction in MR, a second and third MitraClip device may be placed to further reduce MR. Device is placed on mitral valve leaflets. Guideline-directed medical therapy consistent with each patient's condition during follow-up. Duration 24 months. Concurrent medication/care: IV broad-sprectrum antibiotics recommended 1 h prior to and 6-12 h after procedure. Loading dose of

	clopidogrel (≥300 mg) recommended within 24 h prior to procedure or immediately following procedure. Aspirin may also be used at operator discretion. If aspirin used, loading dose of 325 mg acetylsalicylic acid may be administered either pre or immediately post procedure. Post-procedure chronic anticoagulation established with either daily clopidogrel (75 mg) and/or aspirin (81 mg) for 6 months or longer, or if patient has another indication for oral anticoagulation (warfarin or DOACs) these agents may be administered. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Not applicable (NA as no valve repair performed rather than valve replacement). (n=312) Intervention 2: Conservative management - Pharmacological management. Guideline-directed medical therapy consistent with each patient's condition during follow-up. Duration 24 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (NA as no transcatheter procedure performed). 2. Valve type: Not applicable (NA as no valve replacement performed).
Funding	Study funded by industry (Sponsored by Abbott)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR + MEDICAL TREATMENT (MITRACLIP + GUIDELINE-DIRECTED MEDICAL TREATMENT) versus PHARMACOLOGICAL MANAGEMENT (GUIDELINE-DIRECTED MEDICAL TREATMENT)

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral regurgitation: All-cause mortality at 24 months; Group 1: n=302 ; Group 2: n=312; HR 0.62; Lower CI 0.46 to Upper CI 0.82
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Mitral regurgitation: All-cause mortality at 24 months; Group 1: 80/302, Group 2: 121/312; Comments: Note ITT population assuming none missing had event, as missing data not stated.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral regurgitation: Cardiovascular cause of mortality at 24 months; Group 1: 61/302, Group 2: 97/312; Comments: Note ITT

population assuming none missing had event, as missing data not stated.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Mitral regurgitation: Cardiovascular cause of mortality at 24 months; Group 1: Observed events 61 n=302 ; Group 2: Observed events 97 n=312; HR 0.59; Lower CI 0.43 to Upper CI 0.81; Test statistic: P-value: 0.001
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Quality of life at ≥12 months
- Actual outcome for Mitral regurgitation: KCCQ overall summary score at 24 months; Group 1: mean 70.9 (SD 23.8); n=128, Group 2: mean 61.2 (SD 24.4); n=90; KCCQ overall summary score 0-100 Top=High is good outcome; Comments: Baseline values, mean (SD, n): transcatheter repair + medical treatment, 53.2 (22.8, n=302); medical treatment only, 51.6 (23.3, n=309)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Outcome at baseline is comparable. ; Group 1 Number missing: 174; Group 2 Number missing: 222
- Actual outcome for Mitral regurgitation: SF-36 physical component summary at 24 months; Group 1: mean 38.1 (SD 10.2); n=127, Group 2: mean 34.1 (SD 10.2); n=90; SF-36 physical component summary score 0-100 Top=High is good outcome; Comments: Baseline values, mean (SD, n): transcatheter repair + medical treatment, 33.0 (9.0, n=302); medical treatment only, 32.6 (10.0, n=309)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Outcome at baseline is comparable. ; Group 1 Number missing: 175; Group 2 Number missing: 222
- Actual outcome for Mitral regurgitation: SF-36 mental component summary at 24 months; Group 1: mean 50.1 (SD 12.6); n=127, Group 2: mean 48.9 (SD 11.7); n=90; SF-36 mental component summary 0-100 Top=High is good outcome; Comments: Baseline values, mean (SD, n): transcatheter repair + medical treatment, 46.7 (12.7, n=302); medical treatment only, 45.4 (13.0, n=309)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Outcome at baseline is comparable. ; Group 1 Number missing: 175; Group 2 Number missing: 222

Protocol outcome 4: Onset or exacerbation of heart failure at ≥12 months
- Actual outcome for Mitral regurgitation: One or more hospitalisations for heart failure during follow-up at Follow-up (median 22.7 vs. 16.5 months); Group 1: 92/302, Group 2: 151/312
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Outcome at baseline is comparable. ; Group 1 Number

missing: ; Group 2 Number missing: Protocol outcome 5: Intervention-related stroke or TIA at 30 days - Actual outcome for Mitral regurgitation: Stroke at 30 days; Group 1: 2/302, Group 2: 0/312 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness ; Blinding details: If outcome assessors not blinded to intervention could affect diagnosis of stroke event; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Need for re-intervention at ≥12 months - Actual outcome for Mitral regurgitation: Unplanned mitral valve intervention at 24 months; Group 1: 10/302, Group 2: 15/312; Comments: Note ITT population assuming none missing had event, as missing data not stated. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: If outcome assessors not blinded to intervention then could affect likelihood of suggesting subsequent intervention; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Mitral regurgitation: Unplanned mitral valve intervention at 24 months; Group 1: Observed events 10 n=302 ; Group 2: Observed events 15 n=312; HR 0.61; Lower CI 0.27 to Upper CI 1.36; Test statistic: P-value: 0.23 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Blinding details: If outcome assessors not blinded to intervention then could affect likelihood of suggesting subsequent intervention; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Re-hospitalisation at ≥12 months - Actual outcome for Mitral regurgitation: All-cause hospitalisation at 24 months; Group 1: 194/302, Group 2: 228/312; Comments: Note ITT population assuming none missing had event, as missing data not stated. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Mitral regurgitation: All-cause hospitalisation at 24 months; Group 1: Observed events 194 n=302 ; Group 2: Observed events 228 n=312; HR 0.77; Lower CI 0.64 to Upper CI 0.93; Test statistic: P-value: 0.01 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Interevention-related mortality at 30 days; Intervention-related major bleeding at 30 days; Length of hospital stay at after intervention; Intervention-related pacemaker implantation at 30 days; Intervention-

	related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Major vascular complications at 30 days; Renal failure at 30 days

Study (subsidiary papers)	**SURTAVI trial: Reardon 2017[311] (Amrane 2019[12], Durko 2018[107], Serruys 2018[342], Reardon 2019[309], Sondergaard 2019[361], Van mieghem 2020[406])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1746)
Countries and setting	Conducted in Denmark, Germany, Netherlands, Switzerland, USA; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clear echocardiographic parameters for severe aortic stenosis
Stratum	Aortic stenosis (non-bicuspid)
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic, severe aortic stenosis determined by the local multi-disciplinary heart team to be at intermediate surgical risk (an estimated risk of 30-day surgical death of 3-15% according to the STS-PROM). Severe aortic stenosis defined as an initial aortic valve area of 1cm² or less or an aortic valve area index of less than 0.6cm² per square meter of body surface area and a mean gradient of more than 40mmHg or a maximum aortic velocity of more than 4m/s at rest or with dobutamine provocation in patients with a left ventricular ejection fracture of less than 0.25 on resting echocardiography.
Exclusion criteria	Refusal to have SAVR as a treatment option, any condition considered a contraindication for placement of a bioprosthetic valve, a known hypersensitivity or contraindication to all anticoagulation/antiplatelet regimens, nitinol, or sensitivity to contrast media which cannot be adequately pre-medicated, blood dyscrasias as defined: leukopenia (WBC <1000mm³), thrombocytopenia (platelet count <50,000 cells/mm³), history of bleeding diathesis or coagulopathy, ongoing sepsis (including acute endocarditis), any condition

	considered a contraindication to extracorporeal assistance, any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to randomisation, symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 6 weeks of randomisation, cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical haemodynamic support, recent (within 6 months of randomisation) cerebrovascular accident (CVA) or transient ischaemic attack, acute gastrointestinal bleeding that would preclude anticoagulation, subject refuses a blood transfusion, severe dementia, multivessel coronary artery disease with a Syntax score >22 and/or unprotected left main coronary artery, estimated life expectancy of less than 24 months due to associated non-cardiac comorbid conditions, other medical, social or psychological conditions that in the opinion of the Investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams, currently participating in an investigational drug or another device trial, evidence of an acute MI <30 days before the index procedure, need for emergency surgery for any reason, true porcelain aorta, extensive mediastinal radiation, liver failure, reduced ventricular function with an LVEF <20% as measured by resting echocardiogram, uncontrolled AF (resting HR >120bpm), pregnancy or intent to become pregnant prior to completion of all protocol follow-up requirements, end stage renal disease requiring chronic dialysis or creatinine clearance <20cc/min, pulmonary hypertension (systolic pressure >80mmHg), severe COPD demonstrated by FEV1 <750cc, frailty assessment identifiers, Marfan syndrome or other known connective tissue disease that would necessitate aortic root replacement/intervention, native aortic annulus size <18mm or >29mm per baseline diagnostic imaging, pre-existing prosthetic heart valve in any position, mixed aortic valve disease, severe mitral or severe tricuspid regurgitation, severe mitral stenosis, hypertrophic obstructive cardiomyopathy, echocardiographic or CT evidence of new or untreated intracardiac mass, thrombus or vegetation. Ascending aorta diameter greater than maximum diameter relative to the native aortic annulus size, aortic root angulation (femoral and left subclavian/axillary access >70 degrees or right subclavian/axillary access aortic root angulation >30 degrees), congenital bicuspid or unicuspid valve verified by echocardiography, sinus of Valsalva anatomy that would prevent adequate coronary perfusion, transarterial access would not be able to accomodate an 18Fr sheath
Recruitment/selection of patients	Determined by a multidisciplinary team
Age, gender and ethnicity	Age - Mean (SD): Intervention: 79.9±6.2, control: 79.7±6.1. Gender (M:F): 936:724. Ethnicity: Not stated
Further population details	1. Age: Mixed (Majority 75 years or older, but around 20% under this age limit). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Intermediate (STS-

	PROM intervention: 4.4±1.5, STS-PROM control: 4.5±1.6). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=879) Intervention 1: Transcatheter replacement with biological valves. Majority of patients treated iliofemorally (93.6%) with alternative access including direct aortic and subclavian approaches. Duration N/A - Surgical procedure. Concurrent medication/care: Dual antiplatelet therapy of aspirin (81-100mg) and clopidogrel (75mg) was recommended for 3 months, following with monotherapy was recommended lifelong. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Transfemoral 2. Valve type: Biological (n=867) Intervention 2: Standard surgery replacement with biological or mechanical valves. Conventional surgery. Using bioprosthesis. Duration N/A - surgical procedure. Concurrent medication/care: Dual antiplatelet therapy of aspirin (81-100mg) and clopidogrel (75mg) was recommended for 3 months, following with monotherapy was recommended lifelong. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological
Funding	Study funded by industry (Study supported by Medtronic, including direct funding to the lead author)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPLACEMENT WITH BIOLOGICAL VALVES versus STANDARD SURGERY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 2 years; Group 1: 99/864, Group 2: 84/796; Comments: Final KM results at 2 years for modified ITT population. Estimated number of events from the percentages.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Did not undergo the procedure: n=4 deaths, n=6 withdrew, n=5 physicians withdrew. Does not suggest any further loss to follow-up during follow-up but possible
; Group 2 Number missing: 71, Reason: Did not undergo the procedure: n=4 deaths, n=43 withdrew, n=23 physicians withdrew, n=1 lost to follow-up.

Does not suggest any further loss to follow-up during follow-up but possible

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Death from cardiovascular cause at 2 years; Group 1: 67/864, Group 2: 57/796; Comments: Final KM results at 2 years for modified ITT population. Estimated number of events from the percentages.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Did not undergo the procedure: n=4 deaths, n=6 withdrew, n=5 physicians withdrew. Does not suggest any further loss to follow-up during follow-up but possible

; Group 2 Number missing: 71, Reason: Did not undergo the procedure: n=4 deaths, n=43 withdrew, n=23 physicians withdrew, n=1 lost to follow-up. Does not suggest any further loss to follow-up during
follow-up but possible

Protocol outcome 3: Interevention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Death from any cause at 30 days; Group 1: 18/879, Group 2: 11/867; Comments: Analysed using Bayesian analysis. Estimated number of events from the estimated median percentages. ITT.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Uses Bayesian analysis in ITT population; Group 2 Number missing: 71, Reason: Uses Bayesian analysis in ITT population

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): KCCQ change from baseline at 2 year; Group 1: mean 18.9 (SD 21.2); n=879, Group 2: mean 18.6 (SD 22.9); n=867; KCCQ 0-100 Top=High is good outcome; Comments: Calculated using Bayesian Analysis. Reported in appendix of Van Mieghem 2020 paper as a graph showing change in KCCQ over time. Baseline values: 60.0 vs. 59.9. Number analysed not reported for this outcome at 2 years, though possible data has been imputed for those missing at 2 years as this has been done for other outcomes.

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).

Paper indicates the Bayesian analysis was performed in 1660 patients in the modified intention-to-treat population when all had reached 24 months follow-up. For the primary outcome, data was imputed for those with missing data, but unclear if this also applied to the quality of life outcome. Number with missing data for this outcome is unclear.; Group 2 Number missing: , Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).

Paper indicates the Bayesian analysis was performed in 1660 patients in the modified intention-to-treat population when all had reached 24 months follow-up. For the primary outcome, data was imputed for those with missing data, but unclear if this also applied to the quality of life outcome. Number with missing data for this outcome is unclear.
- Actual outcome for Aortic stenosis (non-bicuspid): SF-36 change (physical summary) at 3 months; Group 1: mean 7.39 (SD 10.47); n=753, Group 2: mean 5.56 (SD 10.49); n=659; SF-36 physical summary 0-100 Top=High is good outcome; Comments: Baseline values not reported.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Less than 12 months; Group 1 Number missing: 126, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention). The appendix reports this number of people included.; Group 2 Number missing: 208, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention). The appendix reports this number of people included.
- Actual outcome for Aortic stenosis (non-bicuspid): EQ-5D change at 3 months; Group 1: mean 0.06 (SD 0.18); n=776, Group 2: mean 0.05 (SD 0.18); n=680; EQ-5D 0-1 Top=High is good outcome; Comments: Baseline values not reported.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Less than 12 months; Group 1 Number missing: 103, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention). The appendix reports this number of people included.; Group 2 Number missing: 187, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention). The appendix reports this number of people included.

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): All stroke and TIA at 30 days; Group 1: 30/879, Group 2: 46/867; Comments: Analysed using Bayesian analysis. Estimated number of events from the estimated median percentages.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: Uses Bayesian analysis in ITT population; Group 2 Number missing: 0, Reason: Uses Bayesian analysis in ITT population

Protocol outcome 6: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Life-threatening or major bleeding at 30 days; Group 1: 104/858, Group 2: 73/784; Comments: Analysed using Bayesian analysis. Estimated number of events from the estimated median percentages.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 21, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention). The appendix reports this number of people included.; Group 2 Number missing: 84, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention). The appendix reports this number of people included.

Protocol outcome 7: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Reintervention at 2 years; Group 1: 21/864, Group 2: 4/796; Comments: Final KM results at 2 years for modified ITT population. Estimated number of events from the percentages.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Did not undergo the procedure: n=4 deaths, n=6 withdrew, n=5 physicians withdrew. Does
not suggest any further loss to follow-up during follow-up but possible; Group 2 Number missing: 71, Reason: Did not undergo the procedure: n=4 deaths, n=43 withdrew, n=23 physicians withdrew,
n=1 lost to follow-up. Does not suggest any further loss to follow-up during
follow-up but possible

Protocol outcome 8: Length of hospital stay at after intervention
- Actual outcome for Aortic stenosis (non-bicuspid): Length of hospital stay at 30 days; Group 1: mean 5.75 days (SD 4.85); n=863, Group 2: mean 9.75 days (SD 8.03); n=795
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 16, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).

; Group 2 Number missing: 72, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).

Protocol outcome 9: Re-hospitalisation at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Aortic valve hospitalisation at 2 years; Group 1: 111/864, Group 2: 76/796; Comments: Final KM results at 2 years for modified ITT population. Estimated number of events from the percentages.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason:
Did not undergo the procedure: n=4 deaths, n=6 withdrew, n=5 physicians withdrew. Does not suggest any further loss to follow-up during follow-up but possible

; Group 2 Number missing: 71, Reason: Did not undergo the procedure: n=4 deaths, n=43 withdrew, n=23 physicians withdrew, n=1 lost to follow-up. Does not suggest any further loss to follow-up during
follow-up but possible

Protocol outcome 10: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Permanent pacemaker implantation at 30 days; Group 1: 224/864, Group 2: 53/796; Comments: Analysed using Bayesian analysis. Estimated number of events from the estimated median percentages.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).
Paper indicates "the primary Bayesian analysis was performed in 1660 patients in the modified intention-to-treat population when 1400 patients had reached 12 months of follow up".; Group 2 Number missing: 71, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).
Paper indicates "the primary Bayesian analysis was performed in 1660 patients in the modified intention-to-treat population when 1400 patients had reached 12 months of follow up".

Protocol outcome 11: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Atrial fibrillation at 30 days; Group 1: 111/864, Group 2: 345/796; Comments: Analysed using Bayesian analysis. Estimated number of events from the estimated median percentages.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).
Paper indicates "the primary Bayesian analysis was performed in 1660 patients in the modified intention-to-treat population when 1400 patients had reached 12 months of follow up".; Group 2 Number missing: 71, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).
Paper indicates "the primary Bayesian analysis was performed in 1660 patients in the modified intention-to-treat population when 1400 patients had reached 12 months of follow up".

Protocol outcome 12: Major vascular complications at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major vascular complication at 30 days; Group 1: 52/864, Group 2: 9/796; Comments: Analysed using Bayesian analysis. Estimated number of events from the estimated median percentages.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 23, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).; Group 2 Number missing: 85, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).

Protocol outcome 13: Renal failure at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Acute kidney injury stage 2 or 3 at 30 days; Group 1: 15/864, Group 2: 35/796; Comments: Analysed using Bayesian analysis. Estimated number of events from the estimated median percentages.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).
Paper indicates "the primary Bayesian analysis was performed in 1660 patients in the modified intention-to-treat population when 1400 patients had reached 12 months of follow up".; Group 2 Number missing: 71, Reason: Uses Bayesian analysis with the modified intention to treat group (only people who received an intervention).
Paper indicates "the primary Bayesian analysis was performed in 1660 patients in the modified intention-to-treat population when 1400 patients had

reached 12 months of follow up".	
Protocol outcomes not reported by the study	Onset or exacerbation of heart failure at ≥12 months; Prosthetic valve endocarditis at ≥12 months

Study (subsidiary papers)	**Thyregod 2015[392] (Gronlykke 2017[147], Jørgensen 2017[174], Ngo 2018[270], Sondergaard 2019[360], Sondergaard 2016[362], Thyregod 2013[390], Thyregod 2016[391], Thyregod 2019[393])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=280)
Countries and setting	Conducted in Denmark, Sweden; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): Up to 6 years depending on outcome
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Specific echocardiographic parameters
Stratum	Aortic stenosis (non-bicuspid)
Subgroup analysis within study	Not applicable
Inclusion criteria	People who are 70 years or older with severe degenerative AV stenosis with symptoms or without symptoms but with left ventricular systolic dysfunction and/or hypertrophy. Patients must be suitable for both TAVI and SAVR according to a cardiac surgeon, an interventionist and an echocardiographer at a multidisciplinary conference.
Exclusion criteria	Previous heart surgery, other significant valve disease, or coronary artery disease requiring revascularisation at the time of referral. Patients with a stroke or TIA within the previous 30 days or an acute coronary syndrome within the previous year are also excluded.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): TAVR: 79.2±4.9, SAVR: 79.0±4.7. Gender (M:F): 148:132. Ethnicity: Not stated

Further population details	1. Age: 75 years or over (With the confidence intervals the age is mostly still above 75 years). 2. Childbearing age: Women not of childbearing age (≥45 years) 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Low (~88% classified as low-risk. STS-PROM TAVR: 2.9±1.6, STS-PROM SAVR: 3.1±1.7, Logistic EuroSCORE TAVR: 8.4±4.0, Logistic EuroSCORE SAVR: 8.9±5.5, Logistic EuroSCORE II: 1.9±1.2, Logistic EuroSCORE II: 2.0±1.3, Additive EuroSCORE TAVR: 7.4±1.4, Additive EuroSCORE SAVR: 7.5±1.4). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	No indirectness
Interventions	(n=145) Intervention 1: Transcatheter replacement with biological valves. CoreValve system. Duration N/A - Surgical procedure. Concurrent medication/care: Patients advised to take clopidogrel (75mg/day) for 3 months and aspirin (75mg/day) lifelong. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Transfemoral (Transfemoral is the preferred route. Left subclavian was the second choice.). 2. Valve type: Biological (n=135) Intervention 2: Standard surgery replacement with biological or mechanical valves. Conventional open heart surgical technique. All patients received bioprosthetic valves. Duration N/A - Surgical procedure. Concurrent medication/care: Patients advised to take clopidogrel (75mg/day) for 3 months and aspirin (75mg/day) lifelong. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Biological
Funding	Academic or government funding (Study funded by the Danish heart foundation. Individual authors are funded by Medtronic.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPLACEMENT WITH BIOLOGICAL VALVES versus STANDARD SURGERY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): All-cause mortality at 6 years; Group 1: 59/139, Group 2: 51/135
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: Of those randomised, 3 died prior to a procedure being attempted, 1 crossed to SAVR prior to a procedure being attempted and 3 converted to SAVR during an attempted TAVR procedure.; Group 2 Number missing: 4, Reason: Of those randomised, 1 died prior to a procedure being attempted, 1 crossed to SAVR prior to a procedure being attempted and 2 did not have the implantation completed.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Cardiovascular mortality at 5 years; Group 1: 30/145, Group 2: 31/135
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Patients lost in the original study (139 remaining in the arm with 1 switching and 7 lost). However, uses Kaplan-Meier estimates to predict the rest of the population.; Group 2 Number missing: 0, Reason: Patients switch in the original study (135 patients with 4 lost and 4 switching). However, uses Kaplan-Meier estimates to predict the rest of the population.

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): All-cause mortality at 30 days; Group 1: 3/139, Group 2: 5/135
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 3 patients died prior to the procedure. Later 3 more patients switched over to the other arm.; Group 2 Number missing: 0, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 1 patient died prior to the procedure. 2 patients were not implanted. 3 patients crossed into this arm from the other arm.

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Neurological events (stroke and TIA) at 30 days; Group 1: 4/139, Group 2: 4/135
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 3 patients died prior to the procedure. Later 3 more patients switched over to the other arm.; Group 2 Number missing: 0, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 1 patient died prior to the procedure. 2 patients were not implanted. 3 patients crossed into this arm from the other arm.

Protocol outcome 5: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Major, life threatening or disabling bleeding at 30 days; Group 1: 16/139, Group 2: 28/135
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 1 patient switched into this arm and 1 patient switched over to the

other arm. 3 patients died prior to the procedure. Later 3 more patients switched over to the other arm.; Group 2 Number missing: 0, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 1 patient died prior to the procedure. 2 patients were not implanted. 3 patients crossed into this arm from the other arm.

Protocol outcome 6: Need for re-intervention at ≥12 months
- Actual outcome for Aortic stenosis (non-bicuspid): Aortic valve reintervention at 5 years; Group 1: 3/145, Group 2: 1/135
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Patients lost in the original study (139 remaining in the arm with 1 switching and 7 lost). However, uses Kaplan-Meier estimates to predict the rest of the population.; Group 2 Number missing: 0, Reason: Patients switch in the original study (135 patients with 4 lost and 4 switching). However, uses Kaplan-Meier estimates to predict the rest of the population.

Protocol outcome 7: Length of hospital stay at after intervention
- Actual outcome for Aortic stenosis (non-bicuspid): Length of hospital stay at 30 days; Group 1: mean 8.9 Days (SD 6.2); n=139, Group 2: mean 12.9 Days (SD 11.6); n=135
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 3 patients died prior to the procedure. Later 3 more patients switched over to the other arm.; Group 2 Number missing: 0, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 1 patient died prior to the procedure. 2 patients were not implanted. 3 patients crossed into this arm from the other arm.

Protocol outcome 8: Intervention-related pacemaker implantation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): Permanent pacemaker implantation at 30 days; Group 1: 46/139, Group 2: 2/135
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 3 patients died prior to the procedure. Later 3 more patients switched over to the other arm.; Group 2 Number missing: 0, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 1 patient died prior to the procedure. 2 patients were not implanted. 3 patients crossed into this arm from the other arm.

Protocol outcome 9: Intervention-related atrial fibrillation at 30 days
- Actual outcome for Aortic stenosis (non-bicuspid): New-onset AF at 30 days; Group 1: 24/139, Group 2: 77/135
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 1 patient switched into this arm and 1 patient switched over to the

other arm. 3 patients died prior to the procedure. Later 3 more patients switched over to the other arm.; Group 2 Number missing: 0, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 1 patient died prior to the procedure. 2 patients were not implanted. 3 patients crossed into this arm from the other arm. Protocol outcome 10: Prosthetic valve endocarditis at ≥12 months - Actual outcome for Aortic stenosis (non-bicuspid): Valve endocarditis at 5 years; Group 1: 9/145, Group 2: 6/135 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: Patients lost in the original study (139 remaining in the arm with 1 switching and 7 lost). However, uses Kaplan-Meier estimates to predict the rest of the population.; Group 2 Number missing: 0, Reason: Patients switch in the original study (135 patients with 4 lost and 4 switching). However, uses Kaplan-Meier estimates to predict the rest of the population. Protocol outcome 11: Major vascular complications at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): Major vascular complications at 30 days; Group 1: 8/145, Group 2: 2/135 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 3 patients died prior to the procedure. Later 3 more patients switched over to the other arm.; Group 2 Number missing: 0, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 1 patient died prior to the procedure. 2 patients were not implanted. 3 patients crossed into this arm from the other arm. Protocol outcome 12: Renal failure at 30 days - Actual outcome for Aortic stenosis (non-bicuspid): AKI II/III at 30 days; Group 1: 1/145, Group 2: 9/135 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 3 patients died prior to the procedure. Later 3 more patients switched over to the other arm.; Group 2 Number missing: 0, Reason: 1 patient switched into this arm and 1 patient switched over to the other arm. 1 patient died prior to the procedure. 2 patients were not implanted. 3 patients crossed into this arm from the other arm.
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Re-hospitalisation at ≥12 months

Study	Turi 1991[399]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in India; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 8 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cardiac catheterisation
Stratum	Mitral stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	People with severe rheumatic mitral stenosis in sinus rhythm
Exclusion criteria	Severe pulmonary hypertension, leaflet calcification, subvalvular disease, evidence of left atrial thrombus by echo, and people not suitable for both procedures
Recruitment/selection of patients	Consecutive patients from a cardiology clinic
Age, gender and ethnicity	Age - Mean (SD): Intervention: 27.1±7.6 (range: 14-45), Control: 28.5±10.3 (range: 14-50). Gender (M:F): 16:24. Ethnicity: Not stated
Further population details	1. Age: <75 years (Intervention: 27.1±7.6 (range: 14-45), Control: 28.5±10.3 (range: 14-50)). 2. Childbearing age: Women of childbearing age (<45) (Mean age in both groups less than 45). 3. Morphology (for MS): Morphology suitable for transcatheter intervention (Stated that they require all patients to be suitable for

	transcatheter or surgical intervention). 4. Operative risk (for AS and MR): Not applicable 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable
Indirectness of population	Serious indirectness: Age range includes patients under the age of 18
Interventions	(n=20) Intervention 1: Transcatheter repair. Balloon commissurotomy performed immediately after cardiac catheterisation (used to confirm diagnosis). Used two balloons for each patient checking position through left atrial and ventricular pressures. Duration N/A (surgical procedure). Concurrent medication/care: 9 patients were taking digitalis, 16 were taking diuretics. No other information given. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable (Not aortic stenosis population). 2. Valve type: Biological (n=20) Intervention 2: Minimally invasive surgery repair. Closed mitral commissurotomy by left lateral thoracotomy using a Tubbs dilator inserted by a left ventriculotomy. Duration N/A (surgical procedure). Concurrent medication/care: 12 patients were taking digitalis, 18 were taking diuretics. No additional information available. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not applicable
Funding	Equipment / drugs provided by industry (Equipment provided by various organisations, including Mansfield Scientific, Namic, Cordis, Elecath, Mallinckrodt, Arrow, Mars White Knight, and Cook Corporations.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR versus MINIMALLY INVASIVE SURGERY REPAIR

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 8 months; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Generally the control group has parameters more likely to be associated with a poorer outcome (worse NYHA class scores, more use of concomitant treatment, worse echocardiographic parameters).; Group 1 Number missing: 1, Reason: 1 complication leading to withdrawal from the study (haemothorax - reported in data). 1 patient had emergency mitral valve replacement after

developing severe mitral regurgitation. 1 patient had a pericardial tamponade and switched over to the surgical arm (though results could be interpreted separately so is not counted as switching in this evaluation).; Group 2 Number missing: 0

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mitral stenosis: Deaths at 8 months; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Generally the control group has parameters more likely to be associated with a poorer outcome (worse NYHA class scores, more use of concomitant treatment, worse echocardiographic parameters).; Group 1 Number missing: 1, Reason: 1 complication leading to withdrawal from the study (haemothorax - reported in data). 1 patient had emergency mitral valve replacement after developing severe mitral regurgitation. 1 patient had a pericardial tamponade and switched over to the surgical arm (though results could be interpreted separately so is not counted as switching in this evaluation).; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Mitral stenosis: Deaths at 30 days; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Generally the control group has parameters more likely to be associated with a poorer outcome (worse NYHA class scores, more use of concomitant treatment, worse echocardiographic parameters).; Group 1 Number missing: 1, Reason: 1 complication leading to withdrawal from the study (haemothorax - reported in data). 1 patient had emergency mitral valve replacement after developing severe mitral regurgitation. 1 patient had a pericardial tamponade and switched over to the surgical arm (though results could be interpreted separately so is not counted as switching in this evaluation).; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Mitral stenosis: Strokes at 30 days; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Generally the control group has parameters more likely to be associated with a poorer outcome (worse NYHA class scores, more use of concomitant treatment, worse echocardiographic parameters).; Group 1 Number missing: 1, Reason: 1 complication leading to withdrawal from the study (haemothorax - reported in data). 1 patient had emergency mitral valve replacement after developing severe mitral regurgitation. 1 patient had a pericardial tamponade and switched over to the surgical arm (though results could be interpreted separately so is not counted as switching in this evaluation); Group 2 Number missing: 0

Protocol outcome 5: Intervention-related major bleeding at 30 days
- Actual outcome for Mitral stenosis: Haemothorax at 30 days; Group 1: 1/20, Group 2: 0/20

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Generally the control group has parameters more likely to be associated with a poorer outcome (worse NYHA class scores, more use of concomitant treatment, worse echocardiographic parameters).; Group 1 Number missing: 1, Reason: 1 complication leading to withdrawal from the study (haemothorax - reported in data). 1 patient had emergency mitral valve replacement after developing severe mitral regurgitation. 1 patient had a pericardial tamponade and switched over to the surgical arm (though results could be interpreted separately so is not counted as switching in this evaluation).; Group 2 Number missing: 0 Protocol outcome 6: Need for re-intervention at ≥12 months - Actual outcome for Mitral stenosis: Re-intervention at 8 months; Group 1: 1/20, Group 2: 0/20; Comments: 1 patient in transcatheter repair group underwent uncomplicated placement of Bjork-Shiley prosthetic valve due to development of severe mitral regurgitation. Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Generally the control group has parameters more likely to be associated with a poorer outcome (worse NYHA class scores, more use of concomitant treatment, worse echocardiographic parameters).; Group 1 Number missing: 1, Reason: 1 complication leading to withdrawal from the study (haemothorax - reported in data). 1 patient had emergency mitral valve replacement after developing severe mitral regurgitation. 1 patient had a pericardial tamponade and switched over to the surgical arm (though results could be interpreted separately so is not counted as switching in this evaluation).; Group 2 Number missing: 0 Protocol outcome 7: Major vascular complications at 30 days - Actual outcome for Mitral stenosis: Haemothorax and/or pericardial tamponade due to the procedure at 30 days; Group 1: 3/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Generally the control group has parameters more likely to be associated with a poorer outcome (worse NYHA class scores, more use of concomitant treatment, worse echocardiographic parameters).; Group 1 Number missing: 1, Reason: 1 complication leading to withdrawal from the study (haemothorax - reported in data). 1 patient had emergency mitral valve replacement after developing severe mitral regurgitation. 1 patient had a pericardial tamponade and switched over to the surgical arm (though results could be interpreted separately so is not counted as switching in this evaluation).; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Length of hospital stay at after intervention; Re-hospitalisation at ≥12 months; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Prosthetic valve endocarditis at ≥12 months; Renal failure at 30 days

Study	Vukovic 2019[413]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Serbia; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Preoperative assessment including echocardiography (reports mean systolic gradient)
Stratum	Mixed/unclear aortic valve disease
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing elective isolated aortic valve replacement
Exclusion criteria	Concomitant procedures other than isolated AVR and urgent surgery
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Intervention: 65±8.9, Control: 67.8±8.7. Gender (M:F): 50:50. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mean age and confidence intervals fall below 75 years of age). 2. Childbearing age: Not stated / Unclear 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Low risk (EuroScore II intervention: 1.87±1.03, EuroScore II control: 1.98±1.8). 5. Primary vs secondary valve disease (for MR and TR): Not applicable 6. Systolic dysfunction (for AR): Not applicable

Indirectness of population	Serious indirectness: Mixed aortic valve disease - proportion of stenosis/regurgitation unclear and unclear if includes bicuspid
Interventions	(n=50) Intervention 1: Minimally invasive surgery replacement with biological or mechanical valves - Ministernotomy replacement with biological or mechanical valve. Reverse J-shaped upper ministernotomy from the sternal notch to the third or fourth intercostal space. Biological prosthesis were used in patients older than 65 years (proportion unknown). Duration N/A - surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (Biological prosthesis were used in patients older than 65 years (proportion unknown).). (n=50) Intervention 2: Standard surgery replacement with biological or mechanical valves - Median sternotomy - replacement with biological or mechanical valves. 20-25cm midline skin incision from the sternal notch and a full-length median sternotomy. Biological prosthesis were used in patients older than 65 years (proportion unknown). Duration N/A - Surgical procedure. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Mixed (Biological prosthesis were used in patients older than 65 years (proportion unknown).).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINISTERNOTOMY REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE versus MEDIAN STERNOTOMY - REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVES

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: Mortality at 2 years; Group 1: 3/49, Group 2: 3/49
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: Mortality at 2 years; Group 1: 2/49, Group 2: 2/49

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Post-procedural mortality at 30 days; Group 1: 1/50, Group 2: 1/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related major bleeding at 30 days
- Actual outcome for Mixed/unclear aortic valve disease: Re-exploration for bleeding at 30 days; Group 1: 1/50, Group 2: 2/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Does not discuss major bleeding that did not require re-intervention; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Need for re-intervention at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: Re-exploration for bleeding at 30 days; Group 1: 1/50, Group 2: 2/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Mixed/unclear aortic valve disease: Surgical debridement of deep sternal wound infection at 30 days; Group 1: 0/50, Group 2: 1/50
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 6: Length of hospital stay at after intervention
- Actual outcome for Mixed/unclear aortic valve disease: Hospital stay at 30 days; Group 1: mean 7.6 Days (SD 2); n=50, Group 2: mean 9.3 Days (SD 4.8); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Re-hospitalisation at ≥12 months
- Actual outcome for Mixed/unclear aortic valve disease: Postoperative hospitalisation at 2 years; Group 1: 5/49, Group 2: 2/49; Comments: I believe there is a typo in the main body of the text stating the five patients in the C group needed rehospitalisation while the table states 5 patients required rehospitalisation in the M group. No way to determine this from what is available.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 8: Intervention-related atrial fibrillation at 30 days - Actual outcome for Mixed/unclear aortic valve disease: AF new onset at 30 days; Group 1: 17/50, Group 2: 13/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 9: Prosthetic valve endocarditis at ≥12 months - Actual outcome for Mixed/unclear aortic valve disease: Prosthetic endocarditis at 2 years; Group 1: 1/50, Group 2: 0/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life at ≥12 months; Onset or exacerbation of heart failure at ≥12 months; Intervention-related stroke or TIA at 30 days; Intervention-related pacemaker implantation at 30 days; Major vascular complications at 30 days; Renal failure at 30 days

Study (subsidiary papers)	**REDUCE FMR trial: Witte 2019[429] (Goldberg 2017[139])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Australia, France, Germany, Poland, Portugal, United Kingdom, USA; Setting: Secondary care

Line of therapy	Not applicable
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: MR confirmed by echocardiography
Stratum	Mitral regurgitation: Functional mitral regurgitation (grade 1+ or above)
Subgroup analysis within study	Not applicable:
Inclusion criteria	Age ≥18 years; symptoms of NYHA II, III or IV; LVEF <50%; LV end-diastolic diameter >55 mm; functional MR grade 2+, 3+ or 4+ despite stable (≥3 month) guideline-directed medical therapy; and ability to complete 6 min walk distance of 150-450 m to confirm exercise limitation while proving capacity for serial 6-min walk testing.
Exclusion criteria	Percutaneous coronary intervention in past 30 days; piror mitral valve surgery; significant organic mitral valve pathology; severe mitral annular calcification; and existing or indication for cardiac resynchronisation therapy.
Recruitment/selection of patients	Unclear if consecutive
Age, gender and ethnicity	Age - Mean (SD): Repair, 70.1 (9.7) years; control, 69.1 (8.9) years. Gender (M:F): Repair, 63/24; control, 24/9. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean age <75 years in both groups). 2. Childbearing age: Women not of childbearing age (≥45 years) (Mean age >45 years in both groups). 3. Morphology (for MS): Not applicable 4. Operative risk (for AS and MR): Not stated / Unclear (Operative risk not mentioned - not stated to be inoperable). 5. Primary vs secondary valve disease (for MR and TR): Secondary (Functional MR, those with substantial organic mitral valve pathology excluded). 6. Systolic dysfunction (for AR): Not applicable

Extra comments	Cause: ischaemic heart disease (67.8% vs. 63.6%), non-ischaemic cardiomyopathy (32.2% vs. 36.4%); diabetes mellitus, 27.6% vs. 36.4%; mean (SD) BMI: 26.7 (5.3) vs. 28.1 (6.2) kg/m²; NYHA class: II (44.8% vs. 48.5%), III (52.9% vs. 51.5%) and IV (2.3% vs. 0%); beta-blockers, 88.5% vs. 97.0%; ACE inhibitor/ARB/ARNi, 90.8% vs. 87.9%; diuretic, 97.7% vs. 100%; MRA diuretic, 62.% vs. 57.6%; median (IQR) NT-proBNP: 2,505 (1,095-4,386) vs. 2,410 (1,151-4,820); device (ICD or PPM), 49.4% vs. 36.4%; atrial fibrillation, 58.6% vs. 60.6%; mean (SD) systolic BP: 118 (16) vs. 119 (19) mmHg; mean (SD) diastolic BP: 71 (11) vs. 67 (13) mmHg; mean (SD) 6 min walk test: 306.4 (90.5) vs. 292.6 (91.5) m; mean (SD) LVEF: 34 (9) vs. 37 (9)%; mean (SD) MR volume: 40.4 (23.9) vs. 38.1 (24.0) ml/beat; MR grade: 1+ (28.7% vs. 32.3%), 2+ (39.1% vs. 25.8%), 3+ (26.4% vs. 35.5%) and 4+ (5.7% vs. 6.5%); mean (SD) creatinine: 112.3 (31.1) vs. 118.8 (34.1) mmol/l.
Indirectness of population	No indirectness
Interventions	(n=87) Intervention 1: Transcatheter repair. Coronary sinus-based mitral annular reduction approach for functional MR. Under general anaesthesia or conscious sedation, coronary angiography performed through radial or femoral access. 10-F sheath inserted into right internal jugular vein and Carillon delivery catheter used to engage the coronary sinus. Intervention group then received device implantation (appropriate sized device inserted into delivery catheter and deployed). Duration Intervention + up to 12 months medical?. Concurrent medication/care: Receiving optimal heart failure medical therapy (optimally tolerated doses of guideline-directed therapy, including beta-blockers, renin-angiotensin-aldosterone system blockers and loop diuretics). Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not stated / Unclear (Unclear). 2. Valve type: Not applicable (n=33) Intervention 2: Conservative management - Pharmacological management. Received sham intervention alongside optimal heart failure medical therapy (optimally tolerated doses of guideline-directed therapy, including beta-blockers, renin-angiotensin-aldosterone system blockers and loop diuretics). Under general anaesthesia or conscious sedation, coronary angiography performed through radial or femoral access. 10-F sheath inserted into right internal jugular vein and Carillon delivery catheter used to engage the coronary sinus. In the control the procedure was then terminated and the sheaths withdrawn. Duration Up to 12 months medical?. Concurrent

	medication/care: Not reported. Indirectness: No indirectness Further details: 1. Route of transcatheter intervention (in TAVI for AS): Not applicable 2. Valve type: Not applicable
Funding	Study funded by industry (Funded by Cardiac Dimensions. Some authors have also received grants from industry.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER REPAIR (CARILLON CONTOUR) versus PHARMACOLOGICAL MANAGEMENT

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Mitral regurgitation: All-cause mortality at 12 months; Group 1: 11/81, Group 2: 5/29
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences between groups remain, including drugs at baseline and proportion in each MR grade; Group 1 Number missing: 6, Reason: Withdrew during follow-up; Group 2 Number missing: 4, Reason: Withdrew during follow-up

Protocol outcome 2: Interevention-related mortality at 30 days
- Actual outcome for Mitral regurgitation: All-cause mortality at 30 days; Group 1: 2/87, Group 2: 0/33; Comments: Both events due to progressive cardiorenal deterioration.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences between groups remain, including drugs at baseline and proportion in each MR grade; Group 1 Number missing: , Reason: Unclear; Group 2 Number missing: , Reason: Unclear

Protocol outcome 3: Quality of life at ≥12 months
- Actual outcome for Mitral regurgitation: Change in KCCQ score from baseline at 12 months; Group 1: mean 9.49 (SD 26.128); n=70, Group 2: mean 7.63 (SD 17.548); n=24; KCCQ score 0-100 Top=High is good outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences between groups remain, including drugs at baseline and proportion in each MR grade; Group 1 Number missing: 17, Reason: Withdrew (n=6) or died (n=11) during follow-up; Group 2 Number missing: 9, Reason: Withdrew (n=4) or died (n=5) during follow-up

Protocol outcome 4: Onset or exacerbation of heart failure at ≥12 months - Actual outcome for Mitral regurgitation: Heart failure exacerbation at 12 months; Group 1: 24/87, Group 2: 11/33 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences between groups remain, including drugs at baseline and proportion in each MR grade; Group 1 Number missing: 6, Reason: Withdrew during follow-up; Group 2 Number missing: 4, Reason: Withdrew during follow-up Protocol outcome 5: Re-hospitalisation at ≥12 months - Actual outcome for Mitral regurgitation: Hospitalisation for heart failure at 12 months; Group 1: 24/87, Group 2: 12/33 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences between groups remain, including drugs at baseline and proportion in each MR grade; Group 1 Number missing: 6, Reason: Withdrew during follow-up; Group 2 Number missing: 4, Reason: Withdrew during follow-up Protocol outcome 6: Prosthetic valve endocarditis at ≥12 months - Actual outcome for Mitral regurgitation: Endocarditis at 12 months; Group 1: 2/87, Group 2: 0/33 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences between groups remain, including drugs at baseline and proportion in each MR grade; Group 1 Number missing: 6, Reason: Withdrew during follow-up; Group 2 Number missing: 4, Reason: Withdrew during follow-up	
Protocol outcomes not reported by the study	Cardiac mortality at ≥12 months; Intervention-related stroke or TIA at 30 days; Intervention-related major bleeding at 30 days; Need for re-intervention at ≥12 months; Length of hospital stay at after intervention; Intervention-related pacemaker implantation at 30 days; Intervention-related atrial fibrillation at 30 days; Major vascular complications at 30 days; Renal failure at 30 days

Appendix E: Forest plots

E.1 Aortic stenosis (non-bicuspid)

E.1.1 Minimally invasive surgery replacement vs. standard surgery replacement

Figure 4: All-cause mortality at ≥12 months

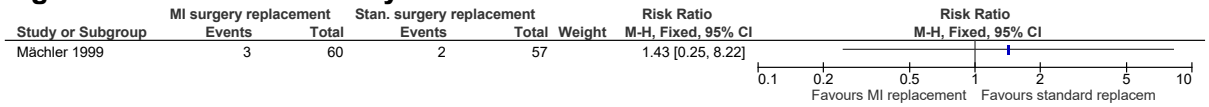


Figure 5: Intervention-related mortality at 30 days

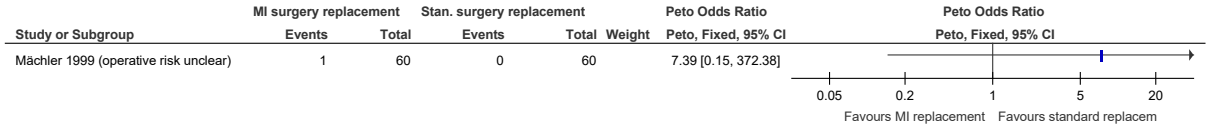


Figure 6: Intervention-related stroke or TIA at 30 days

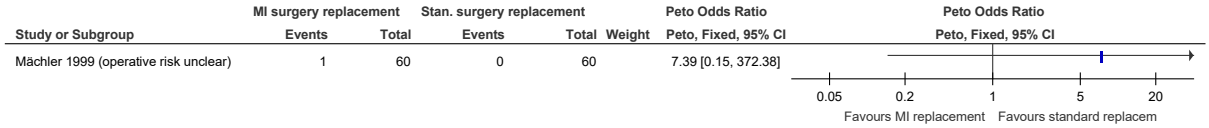


Figure 7: Intervention-related major bleeding (reoperation for bleeding) at 30 days

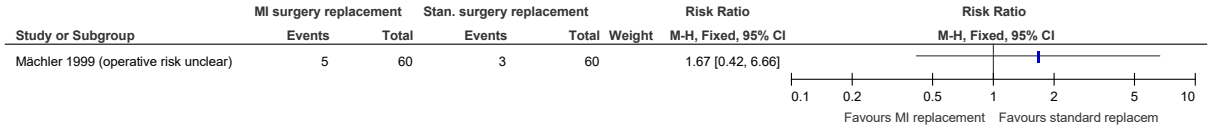


Figure 8: Need for re-intervention (reoperation for paravalvular leakage) at ≥12 months (3 months)

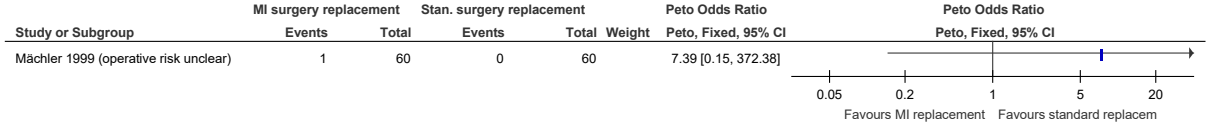
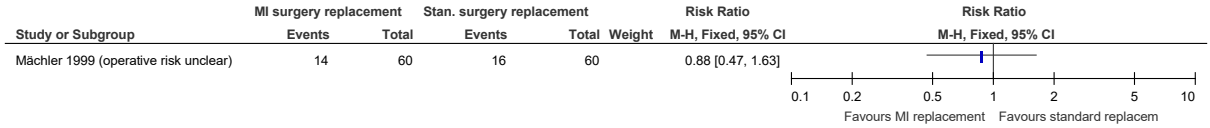


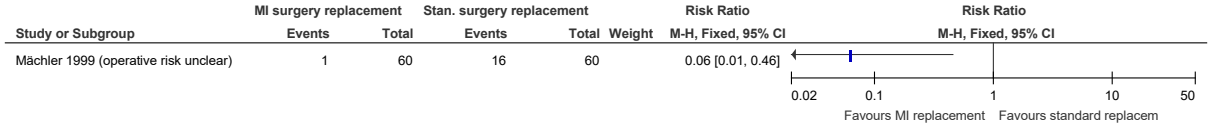
Figure 9: Intervention-related pacemaker implantation (pacing wire implantation) at 30 days



Outcome defined as ventricular or bifocal pacing wires implanted epicardially.

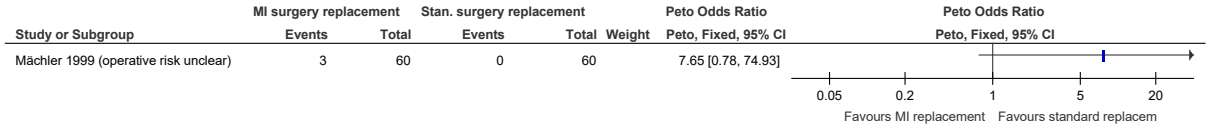
1

Figure 10: Intervention-related AF (supraventricular arrhythmias) at 30 days



2

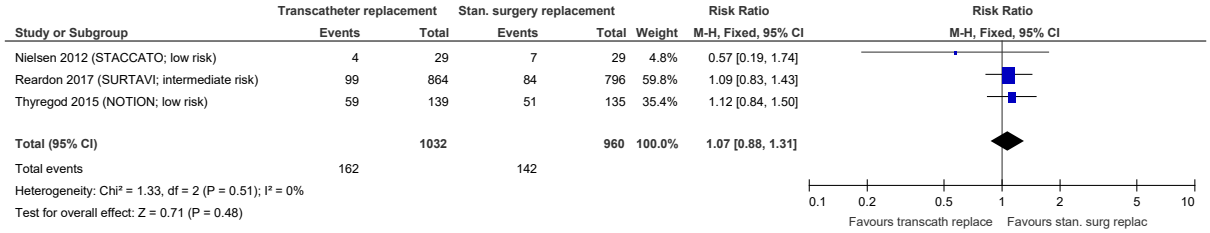
Figure 11: Prosthetic valve endocarditis at ≥12 months



3

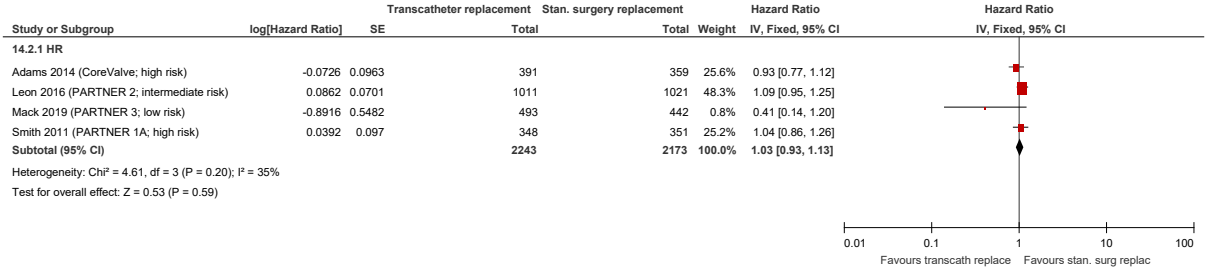
E.142 Transcatheter replacement vs. standard surgery replacement

Figure 12: All-cause mortality at ≥12 months (2-6 years) – studies not reporting time-to-event data



5

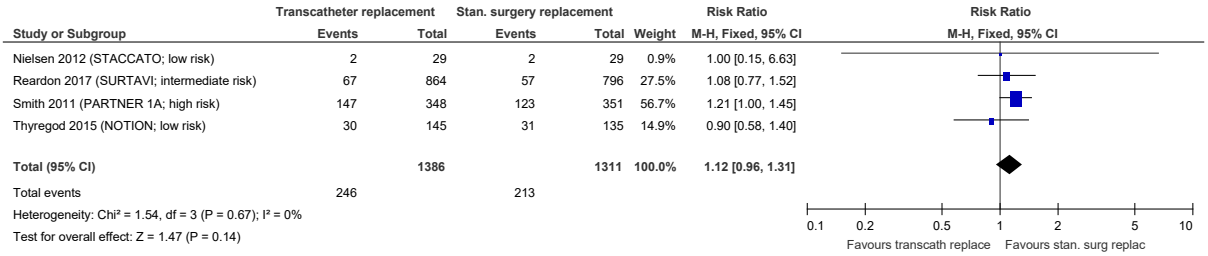
Figure 13: All-cause mortality at ≥12 months (1-5 years) – studies reporting time-to-event data



1

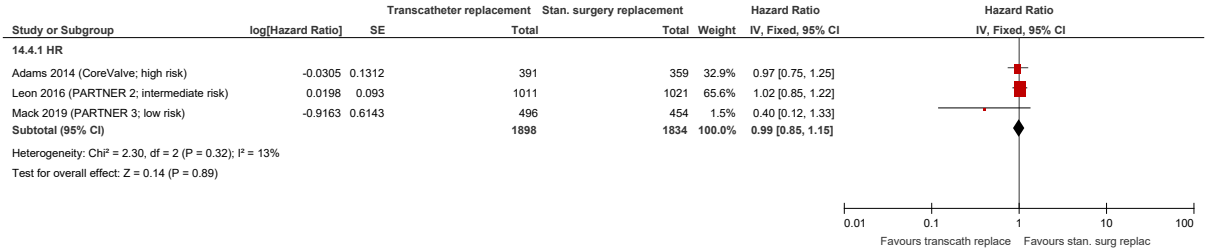
2

Figure 14: Cardiac mortality at ≥12 months (2-5 years) – studies not reporting time-to-event data



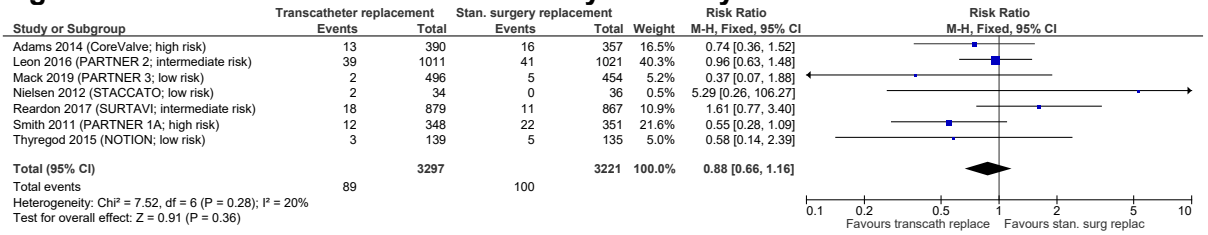
3

Figure 15: Cardiac mortality at ≥12 months (1-5 years) – studies reporting time-to-event data



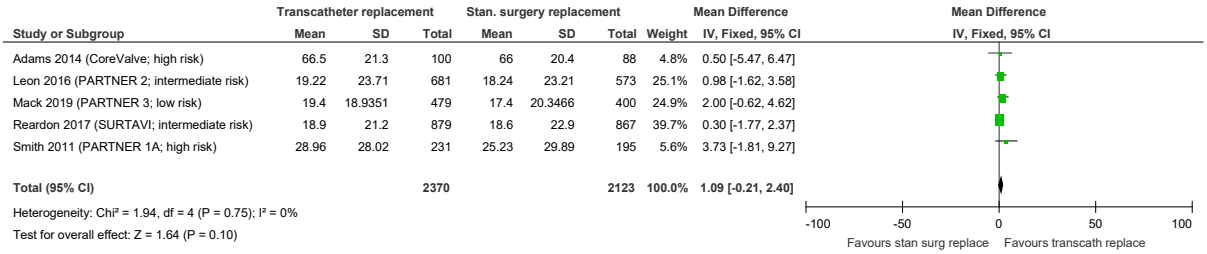
4

Figure 16: Intervention-related mortality at 30 days



1

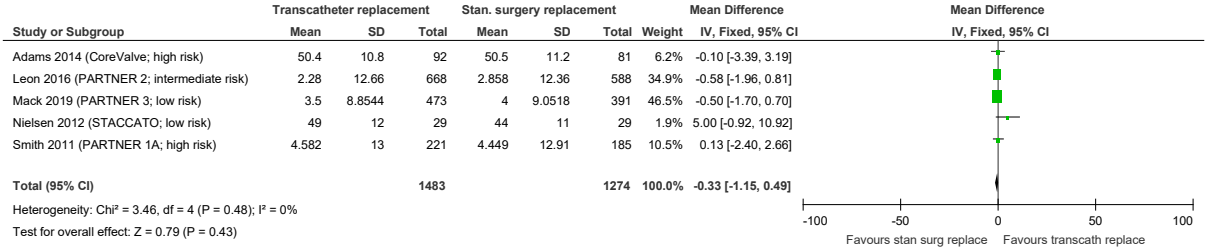
Figure 17: Quality of life (KCCQ summary) at ≥12 months (1-5 years) – mix of change and final scores



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (21.82) by 0.5 and were ±10.91.

2

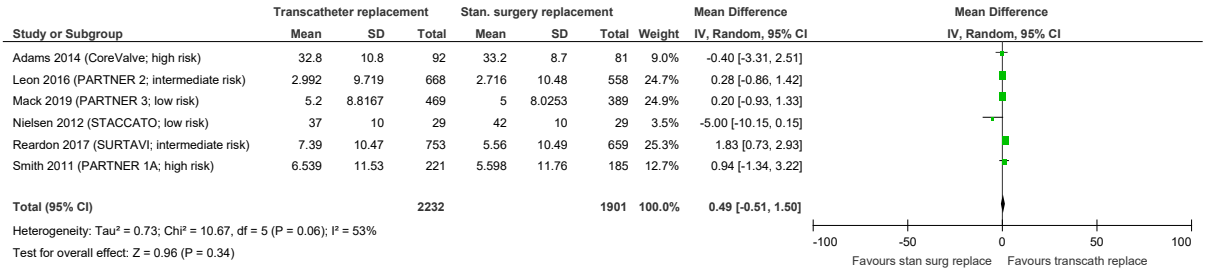
Figure 18: Quality of life (SF-12/SF-36 mental summary) at ≥12 months (1-5 years) – mix of change and final scores



Published MIDs of ±3.0 for the SF-36 mental component score were used to assessed imprecision.

3

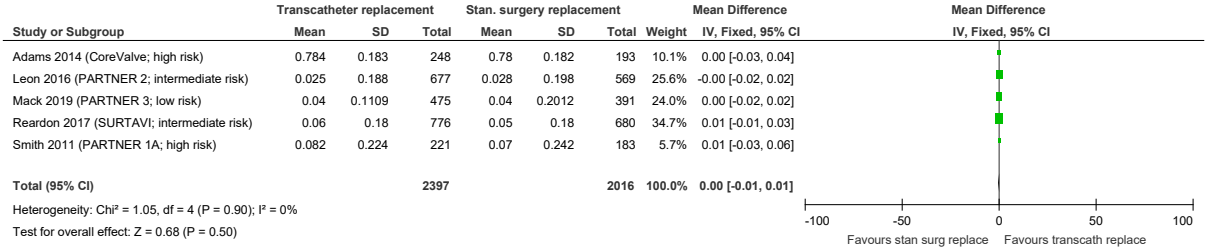
Figure 19: Quality of life (SF-12/SF-36 physical summary) at ≥12 months (3 months - 5 years) – mix of change and final scores



Published MIDs of ±2.0 for the SF-36 physical component score were used to assessed imprecision.

4

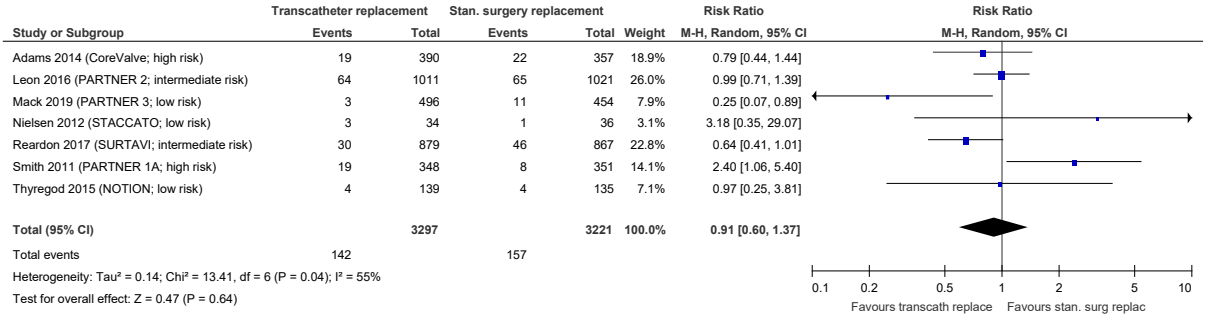
Figure 20: Quality of life (EQ-5D utility) at ≥12 months (3 months - 2 years) – mix of change and final scores



Published MIDs of ±0.03 for EQ-5D on a scale of 0-1 were used to assessed imprecision.

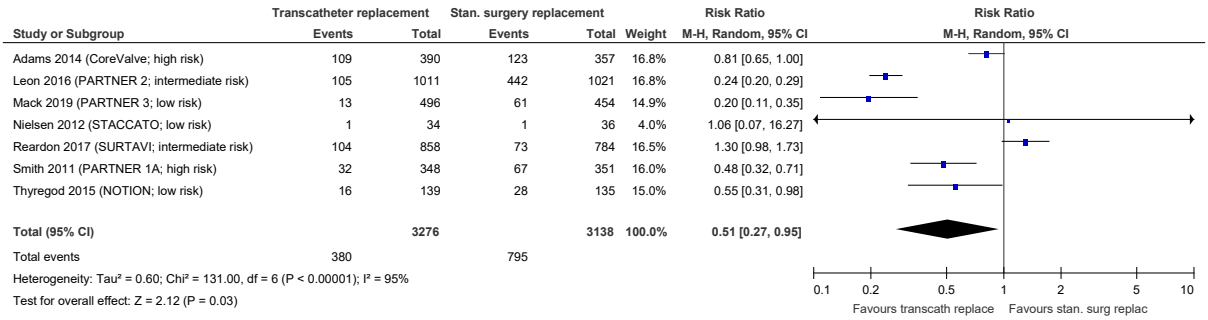
1

Figure 21: Intervention-related stroke or TIA at 30 days



2

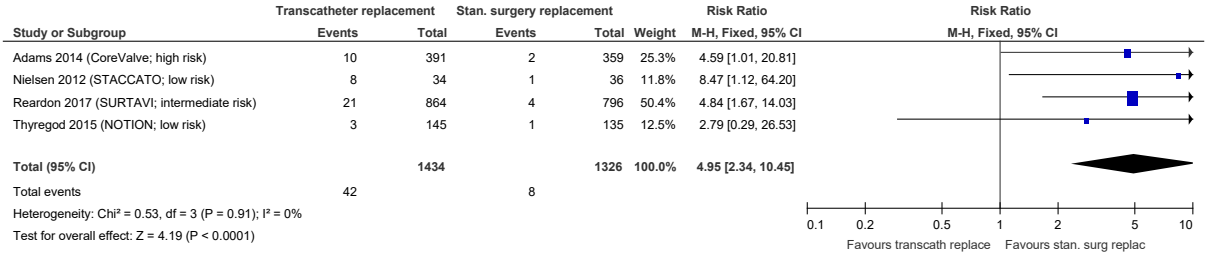
Figure 22: Intervention-related major bleeding at 30 days



3

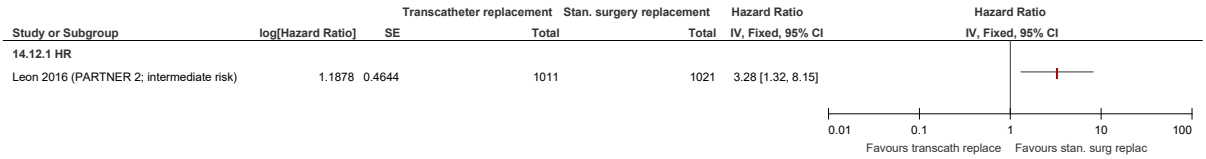
4

Figure 23: Need for re-intervention at ≥12 months (30 days – 5 years) – studies not reporting time-to-event data



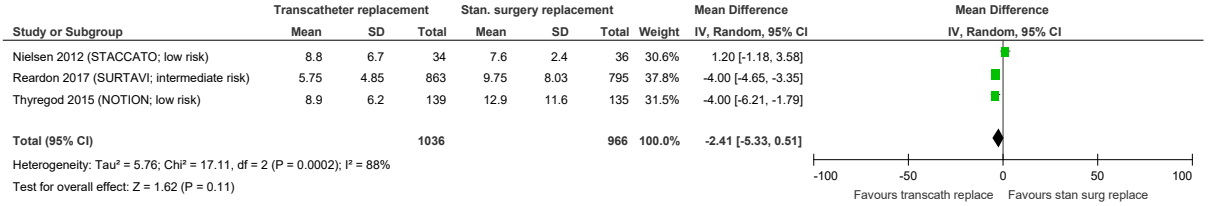
1

Figure 24: Need for re-intervention at ≥12 months (5 years) – studies reporting time-to-event data



2

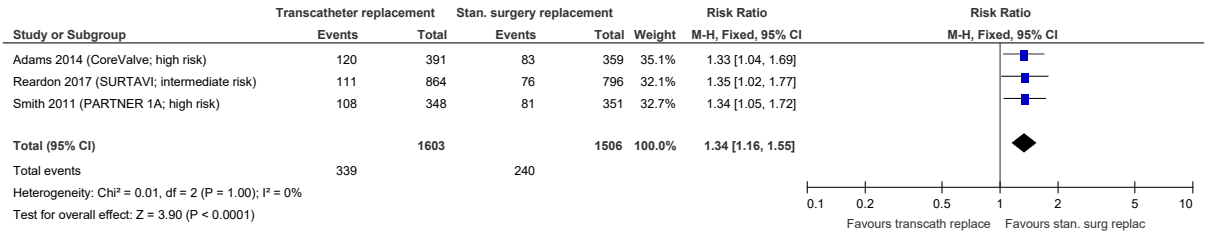
Figure 25: Length of stay post-intervention



MIDs used to assess imprecision were calculated by multiplying the median SD in control groups across studies (8.03) by 0.5 and were ±4.015.

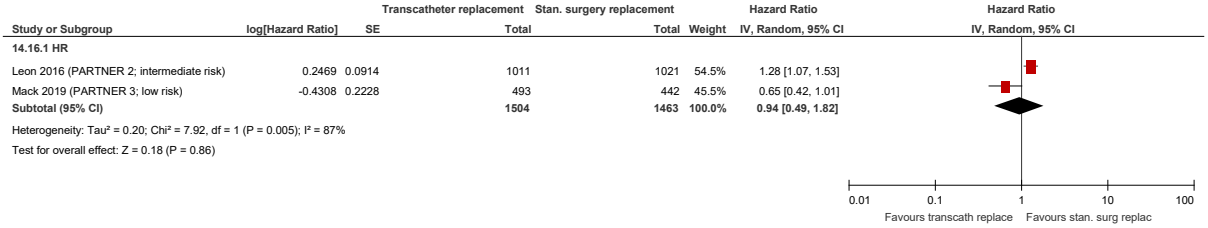
3

Figure 26: Re-hospitalisation at ≥12 months (2-5 years) – studies not reporting time-to-event data



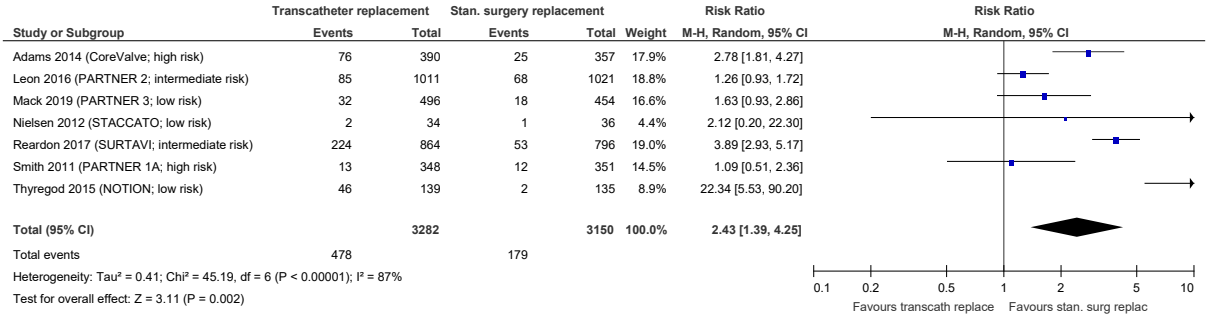
4

Figure 27: Re-hospitalisation at ≥12 months (1-5 years) – studies reporting time-to-event data



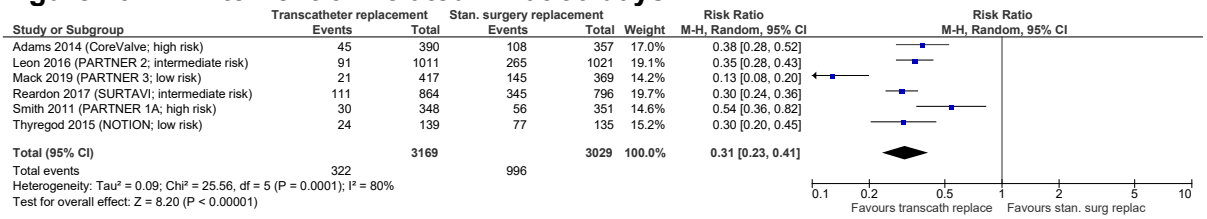
1

Figure 28: Intervention-related pacemaker implantation at 30 days



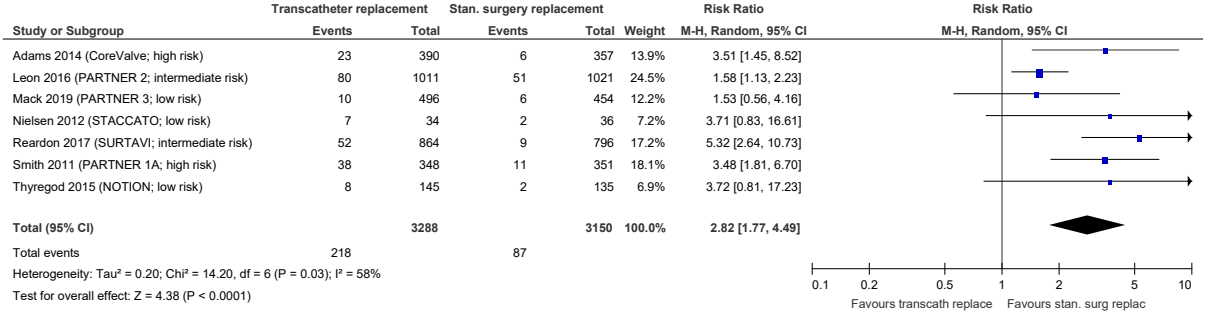
2

Figure 29: Intervention-related AF at 30 days



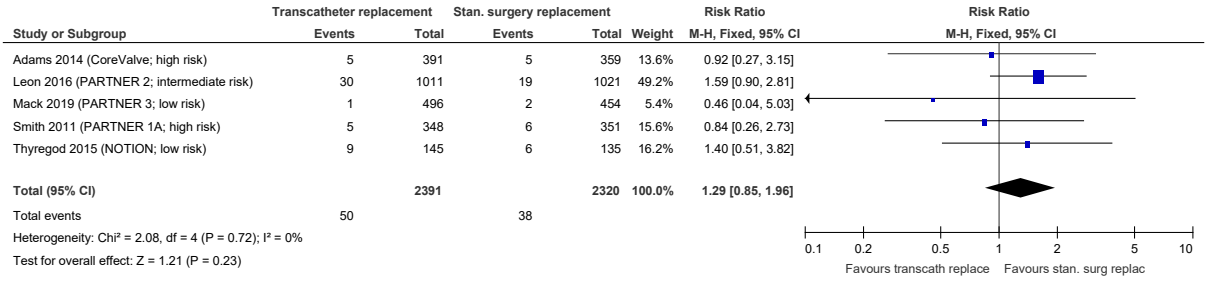
3

Figure 30: Major vascular complications at 30 days



4

Figure 31: Prosthetic valve endocarditis at ≥12 months (1-5 years)

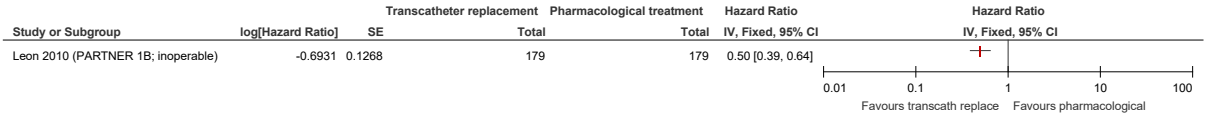


1

2

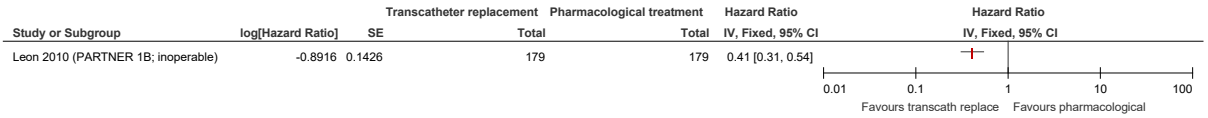
E.13 Transcatheter replacement vs. pharmacological management

Figure 32: All-cause mortality at ≥12 months (5 years) – time-to-event data



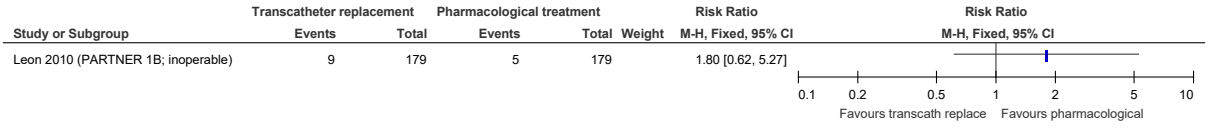
4

Figure 33: Cardiac mortality at ≥12 months (5 years) – time-to-event data



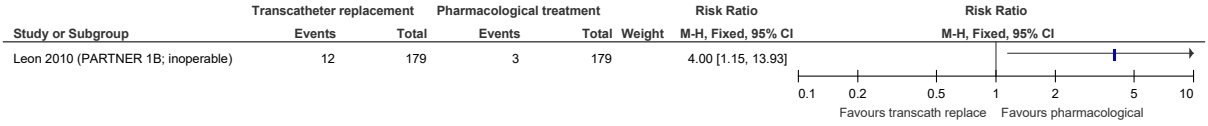
5

Figure 34: Intervention-related mortality at 30 days



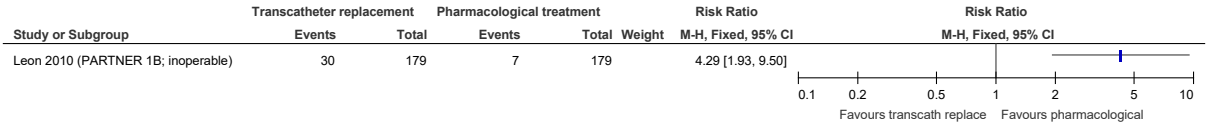
6

Figure 35: Intervention-related stroke or TIA at 30 days



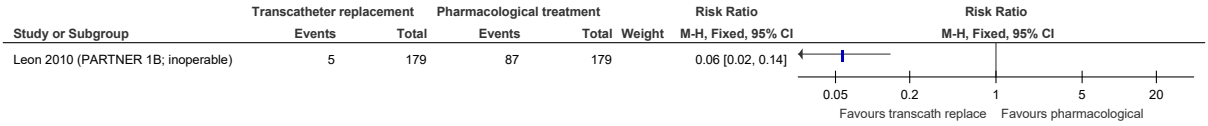
7

Figure 36: Intervention-related major bleeding at 30 days



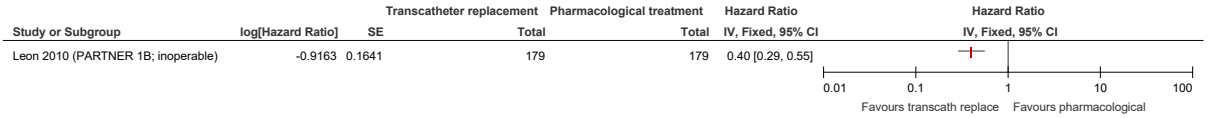
1

Figure 37: Need for re-intervention at ≥12 months (12 months)



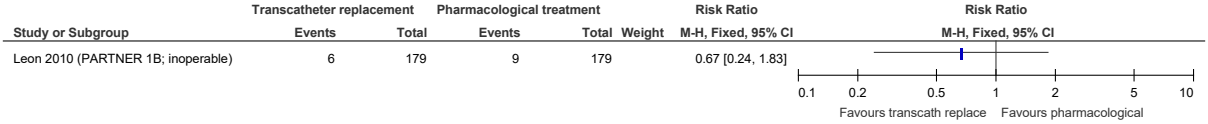
2

Figure 38: Rehospitalisation at ≥12 months (5 years) – time-to-event data



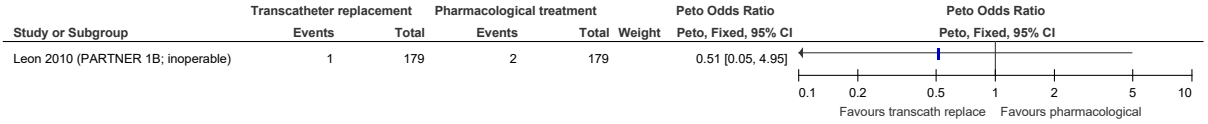
3

Figure 39: Intervention-related pacemaker implantation at 30 days



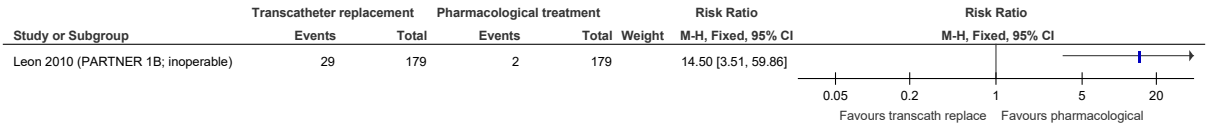
4

Figure 40: Intervention-related atrial fibrillation at 30 days



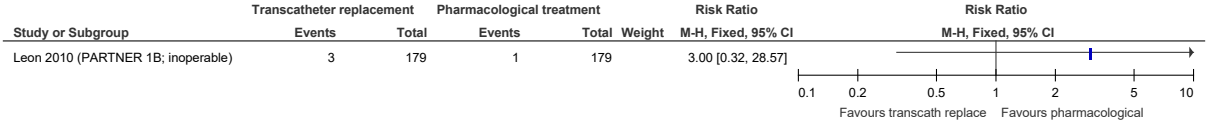
5

Figure 41: Major vascular complications at 30 days



1

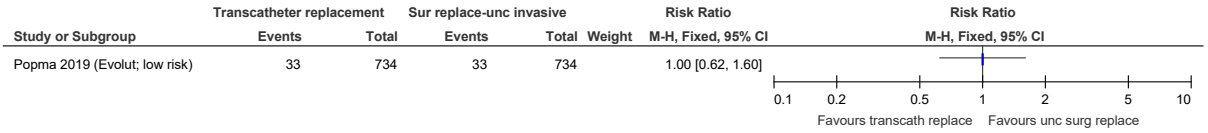
Figure 42: Prosthetic valve endocarditis at ≥12 months (2 years)



2

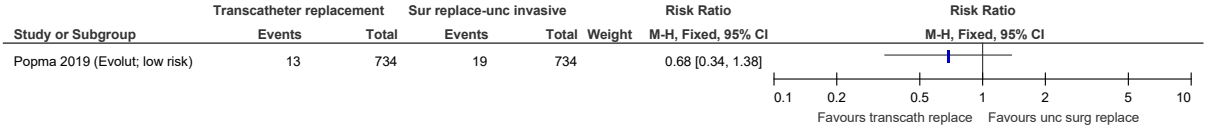
E.13.4 Transcatheter replacement vs. surgery replacement (unclear/mixed invasiveness)

Figure 43: All-cause mortality at ≥12 months (2 years)



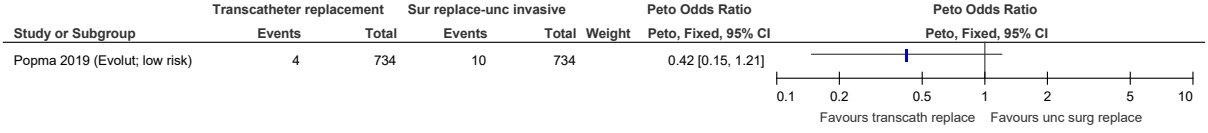
5

Figure 44: Cardiac mortality at ≥12 months (12 months)



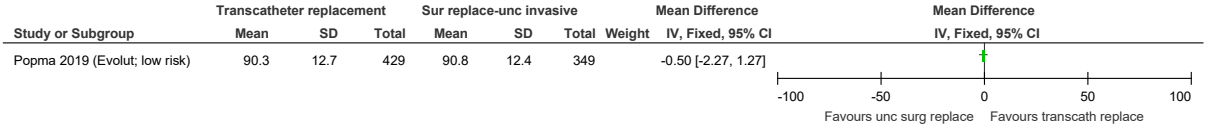
6

Figure 45: Intervention-related mortality at 30 days



7

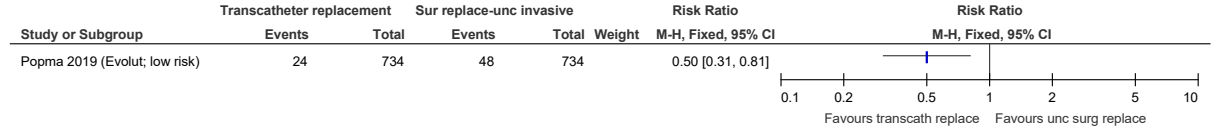
Figure 46: Quality of life (KCCQ summary) at ≥12 months (12 months)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (21.25) by 0.5 and were ±10.63.

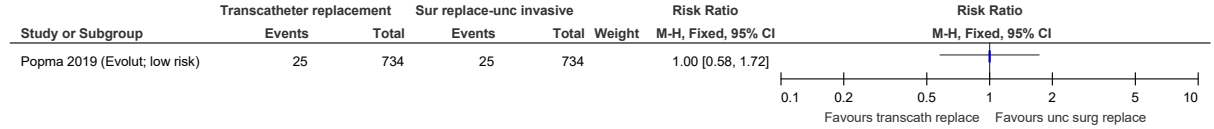
8

Figure 47: Onset or exacerbation of heart failure at ≥12 months (12 months)



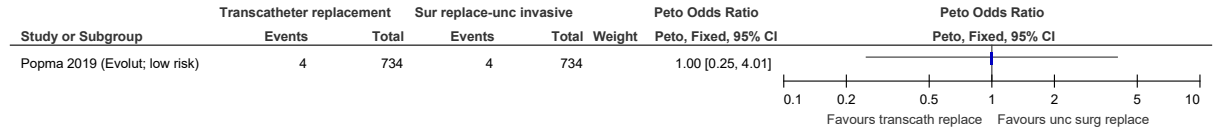
1

Figure 48: Intervention-related stroke or TIA (all stroke) at 30 days



2

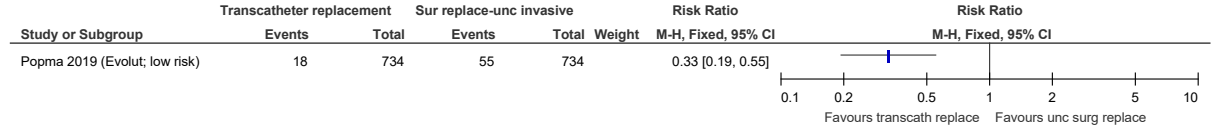
Figure 49: Intervention-related stroke or TIA (TIA) at 30 days



3

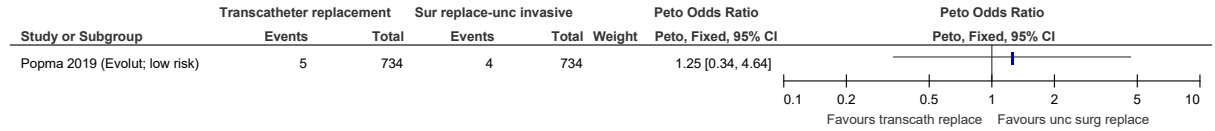
4

Figure 50: Intervention-related major bleeding at 30 days



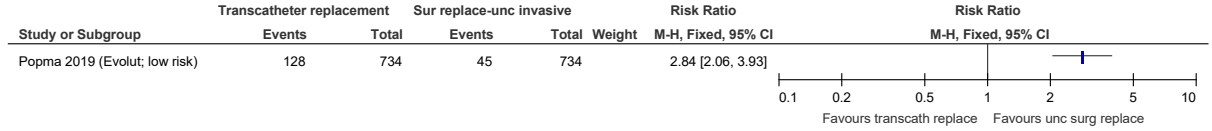
5

Figure 51: Need for re-intervention (aortic re-intervention) at ≥12 months (12 months)



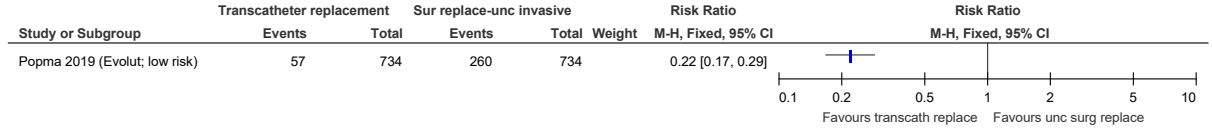
6

Figure 52: Intervention-related pacemaker implantation at 30 days



1

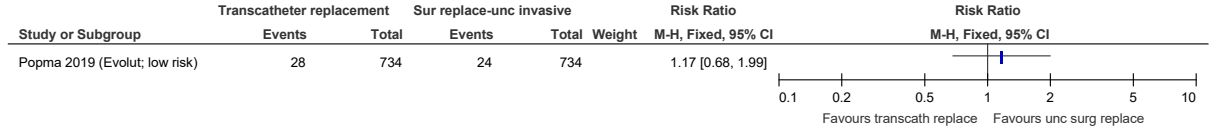
Figure 53: Intervention-related atrial fibrillation at 30 days



2

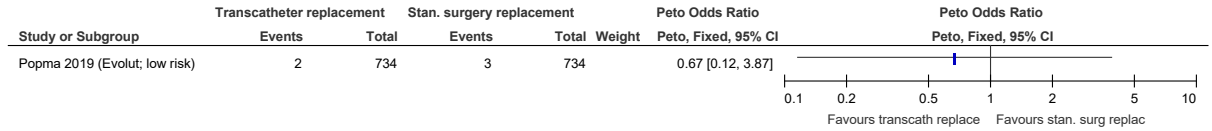
3

Figure 54: Major vascular complications at 30 days



4

Figure 55: Prosthetic valve endocarditis at ≥12 months (12 months)



5

E.2 Aortic stenosis (bicuspid)

7 No evidence was identified for this stratum.

8

E.3 Aortic stenosis (mixed non-bicuspid and bicuspid or unclear)

E.3.1 Minimally invasive surgery replacement vs. standard surgery replacement

Figure 56: All-cause mortality at ≥12 months (12 months)

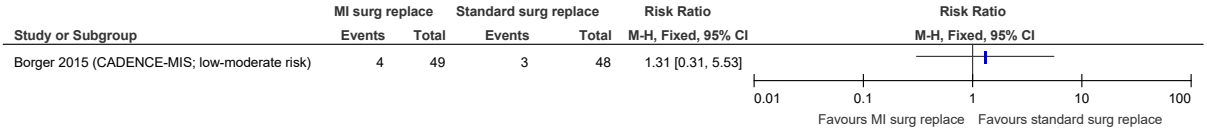


Figure 57: Cardiac mortality at ≥12 months (12 months)

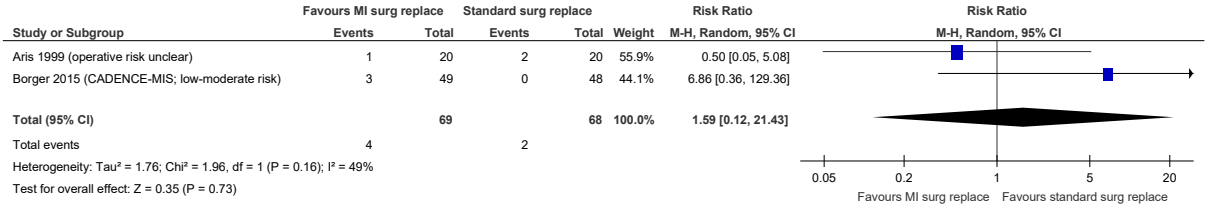


Figure 58: Intervention-related mortality at 30 days

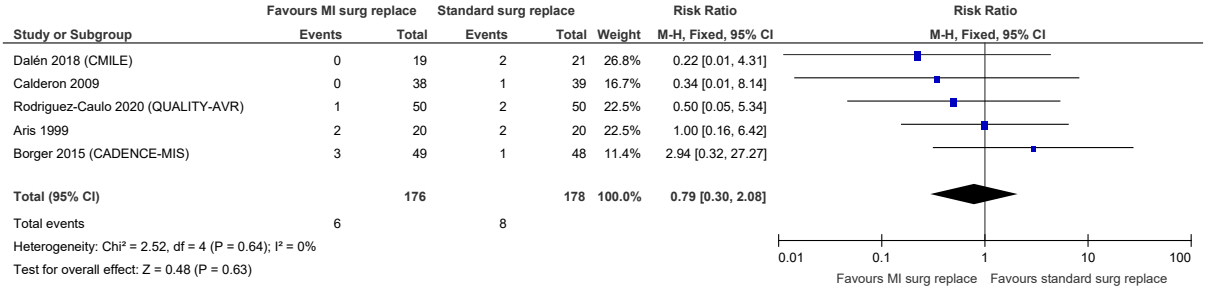
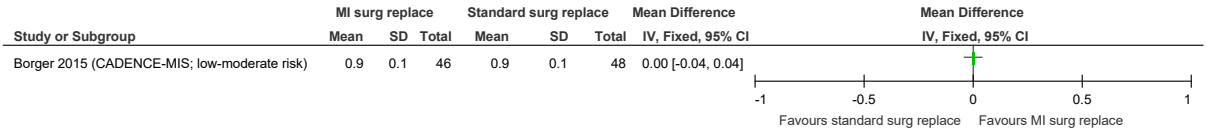
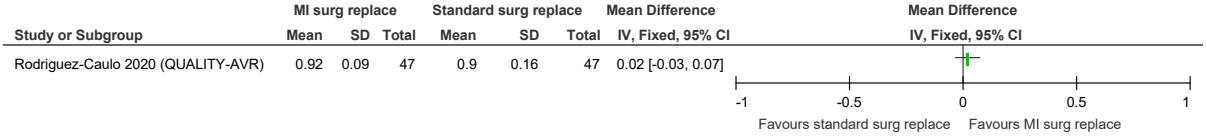


Figure 59: Quality of life (EQ-5D) at ≥12 months (3 months)



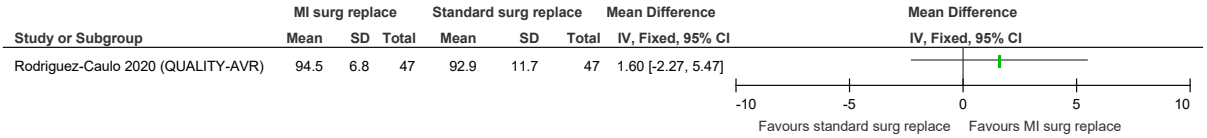
Published MIDs of ±0.03 for EQ-5D on a scale of 0-1 were used to assessed imprecision.

Figure 60: Quality of life (EQ-5D-5L index) at ≥12 months (12 months)



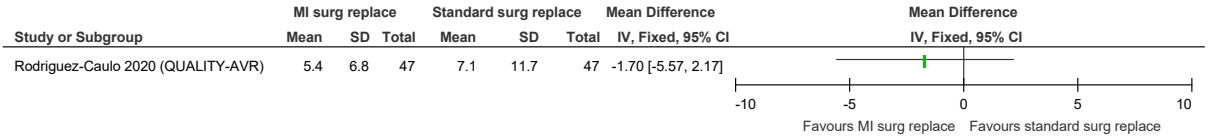
MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (0.15) by 0.5 and were ±0.075.

Figure 61: Quality of life (EQ-5D-5L utilities – health index) at ≥12 months (12 months)



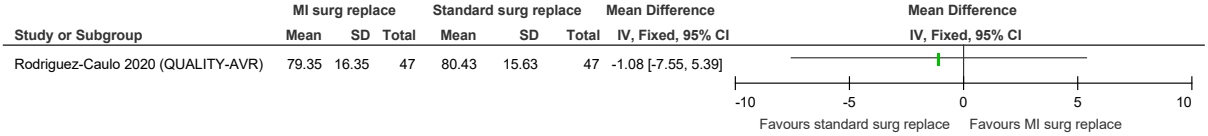
MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (2.05) by 0.5 and were ±1.03.

Figure 62: Quality of life (EQ-5D-5L utilities – severity index) at ≥12 months (12 months)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (12.0) by 0.5 and were ±6.0.

Figure 63: Quality of life (EQ-5D-5L utilities – visual scale) at ≥12 months (12 months)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (14.42) by 0.5 and were ±7.21.

Figure 64: Intervention-related stroke or TIA at 30 days (30 days)

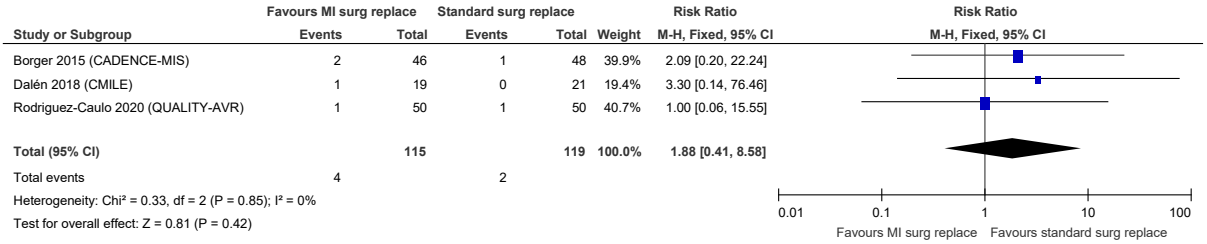


Figure 65: Intervention-related major bleeding at 30 days (72 h – 30 days)

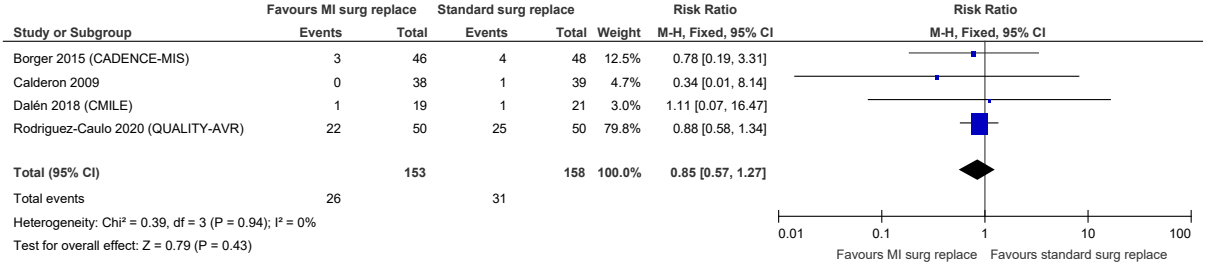


Figure 66: Need for re-intervention at ≥12 months (7-30 days)

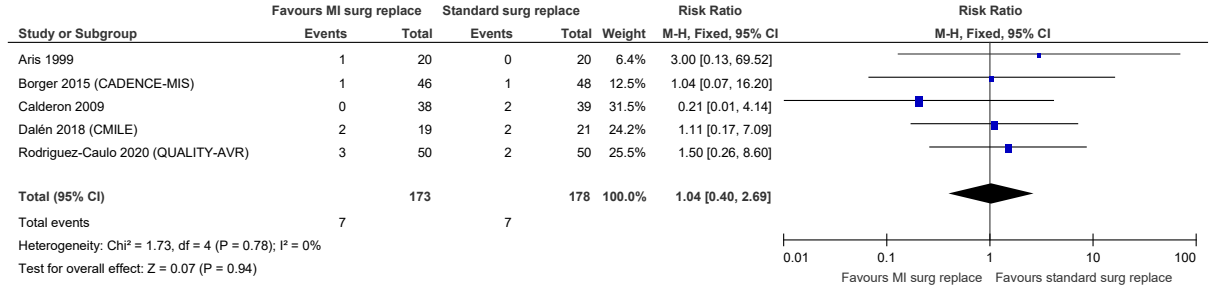
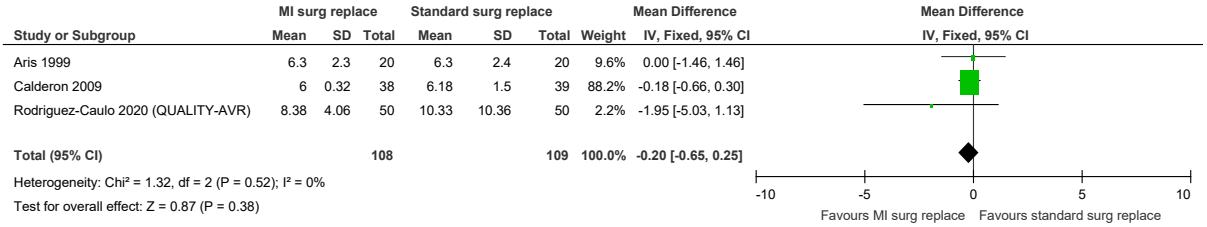
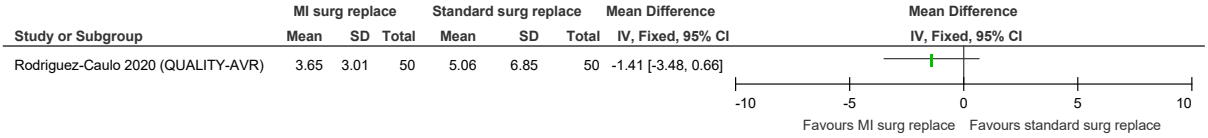


Figure 67: Length of hospital stay (days)



MIDs used to assess imprecision were calculated by multiplying the median SD in control groups across studies (2.4) by 0.5 and were ±1.2.

Figure 68: Length of intensive care unit stay (days)



MIDs used to assess imprecision were calculated by multiplying the median SD in control groups across studies (6.85) by 0.5 and were ±3.425.

Figure 69: Intervention-related pacemaker implantation at 30 days (unclear – 30 days)

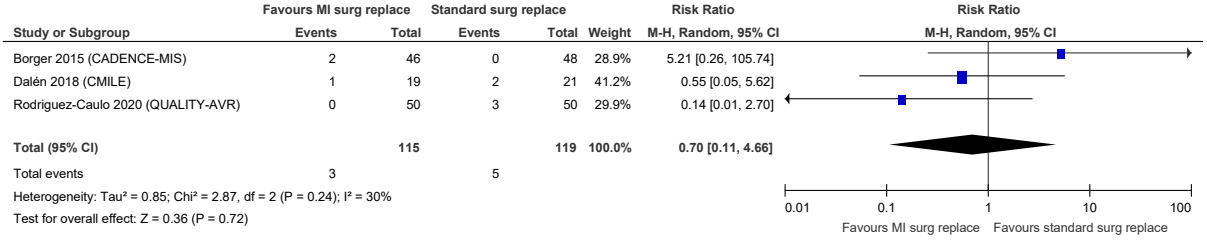


Figure 70: New-onset atrial fibrillation at 30 days (postoperative – 30 days)

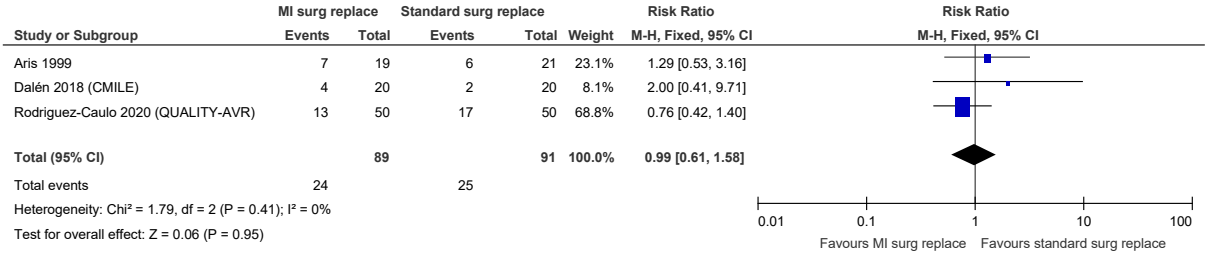
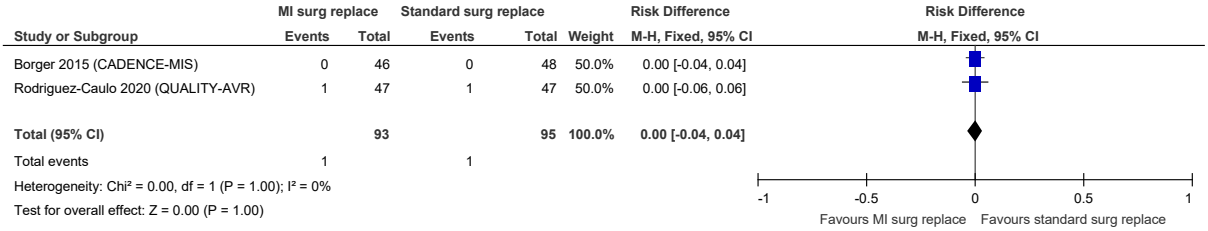


Figure 71: Prosthetic valve endocarditis at ≥12 months (12 months)



E.4 Aortic regurgitation (non-bicuspid)

No evidence was identified for this stratum.

E.5 Aortic regurgitation (bicuspid)

No evidence was identified for this stratum.

E.6 Aortic regurgitation (mixed non-bicuspid and bicuspid or unclear)

No evidence was identified for this stratum.

E.7 Mixed/unclear aortic valve disease

E.7.1 Minimally invasive surgery replacement vs. standard surgery replacement

Figure 72: All-cause mortality at ≥12 months (12-30 months) – studies reporting time-to-event data

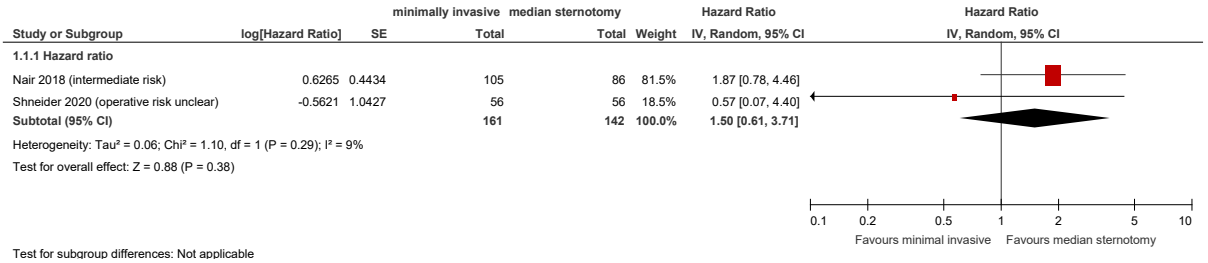


Figure 73: All-cause mortality at ≥12 months (2 years) – studies not reporting time-to-event data

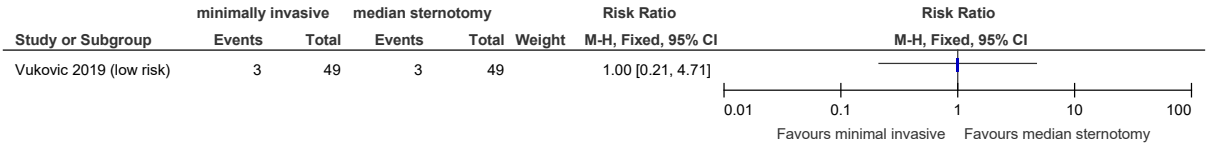


Figure 74: Cardiac mortality at ≥12 months (postoperative – 2 years)

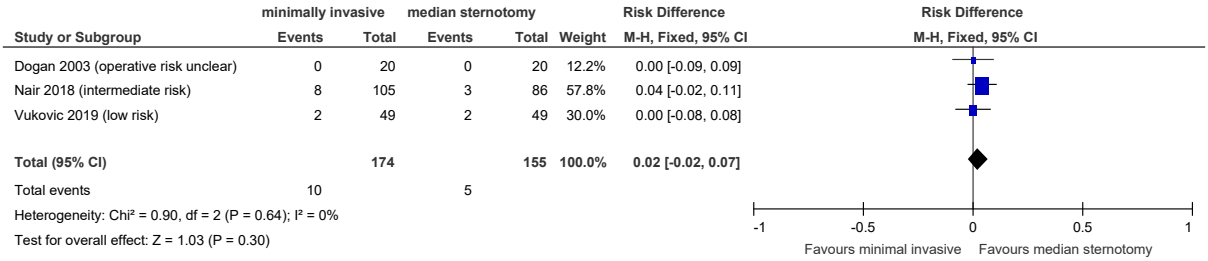


Figure 75: Intervention-related mortality at 30 days (<30 days/in-hospital/postoperative)

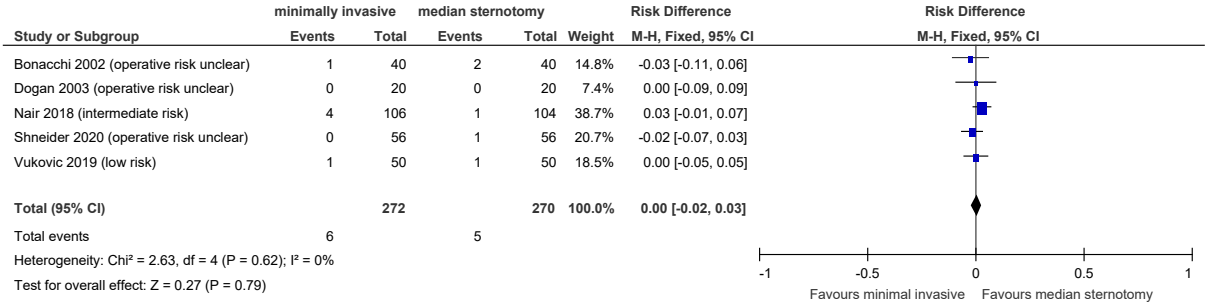
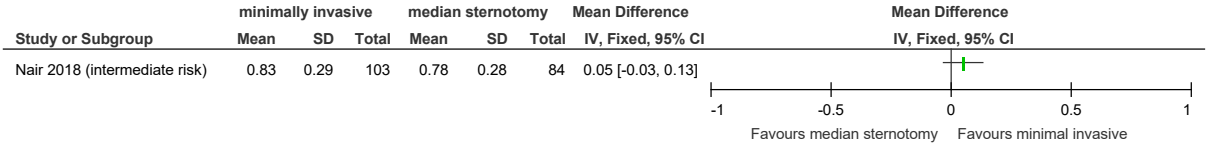


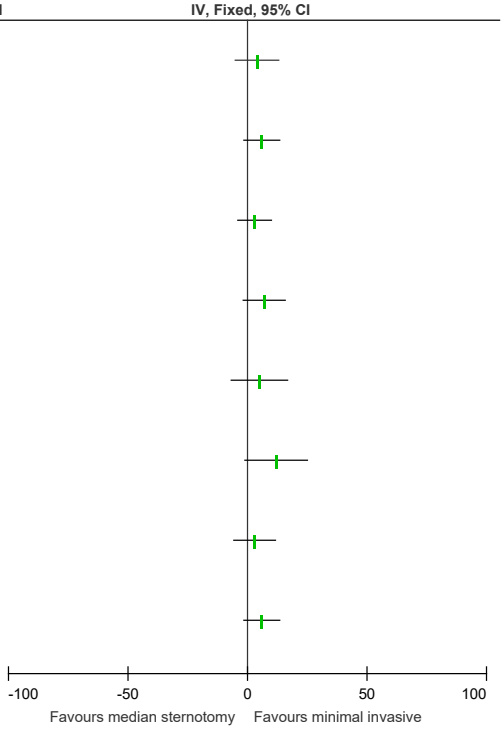
Figure 76: EQ-5D (final value, 0-1, high is good) at ≥12 months (12 months)



Published MIDs of ±0.03 for EQ-5D on a scale of 0-1 were used to assessed imprecision.

Figure 77: SF-36 (final value, 0-100, high is good) at ≥12 months (12 months)

Study or Subgroup	minimally invasive Mean	SD	Total	median sternotomy Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.6.1 Bodily pain							
Nair 2018 (intermediate risk)	76	31	99	72	32	86	4.00 [-5.11, 13.11]
1.6.2 General health							
Nair 2018 (intermediate risk)	68	26	100	62	26	86	6.00 [-1.49, 13.49]
1.6.3 Mental health							
Nair 2018 (intermediate risk)	76	26	100	73	23	86	3.00 [-4.04, 10.04]
1.6.4 Physical functioning							
Nair 2018 (intermediate risk)	74	30	100	67	31	86	7.00 [-1.80, 15.80]
1.6.5 Role emotional							
Nair 2018 (intermediate risk)	76	39	98	71	42	85	5.00 [-6.80, 16.80]
1.6.6 Role physical							
Nair 2018 (intermediate risk)	64	44	98	52	46	85	12.00 [-1.10, 25.10]
1.6.7 Social functioning							
Nair 2018 (intermediate risk)	81	30	98	78	30	85	3.00 [-5.72, 11.72]
1.6.8 Vitality							
Nair 2018 (intermediate risk)	60	26	100	54	26	86	6.00 [-1.49, 13.49]



The following published MIDs for the various domains of the SF-36 questionnaire were used to assessed imprecision: ±4.00 (role emotional), ±3.00 (bodily pain, mental health, physical functioning, role physical and social functioning) and ±2.00 (general health and vitality).

Figure 78: Intervention-related stroke or TIA at 30 days (postoperative)

Study or Subgroup	minimally invasive Events	Total	median sternotomy Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Dogan 2003 (operative risk unclear)	0	20	0	20	26.3%	0.00 [-0.09, 0.09]
Shneider 2020 (operative risk unclear)	0	56	3	56	73.7%	-0.05 [-0.12, 0.01]
Total (95% CI)		**76**		**76**	**100.0%**	**-0.04 [-0.10, 0.02]**
Total events	0		3			
Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 1.38 (P = 0.17)						

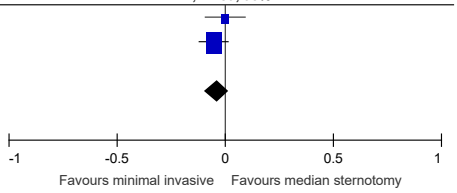


Figure 79: Intervention-related major bleeding (re-exploration for bleeding) at 30 days (<30 days/postoperative)

Study or Subgroup	minimally invasive Events	Total	median sternotomy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bonacchi 2002 (operative risk unclear)	0	40	3	40	25.9%	0.14 [0.01, 2.68]
Dogan 2003 (operative risk unclear)	1	20	1	20	7.4%	1.00 [0.07, 14.90]
Shneider 2020 (operative risk unclear)	2	56	7	56	51.9%	0.29 [0.06, 1.32]
Vukovic 2019 (low risk)	1	50	2	50	14.8%	0.50 [0.05, 5.34]
Total (95% CI)		**166**		**166**	**100.0%**	**0.33 [0.12, 0.95]**
Total events	4		13			
Heterogeneity: Chi² = 1.11, df = 3 (P = 0.78); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						

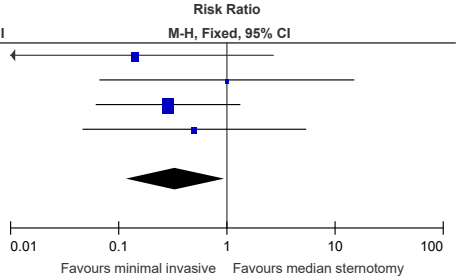


Figure 80: Need for re-intervention at ≥12 months (30 months) – studies reporting time-to-event data

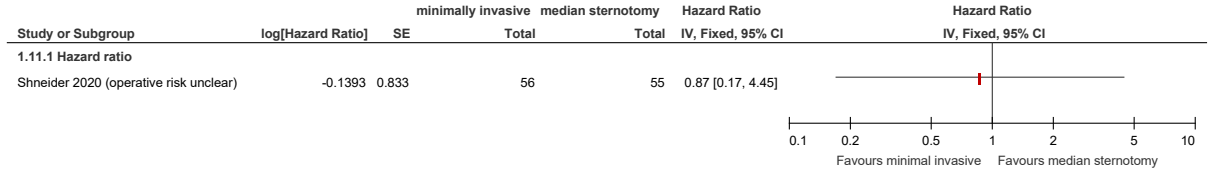


Figure 81: Need for re-intervention at ≥12 months (30 days to 12 months) – studies not reporting time-to-event data

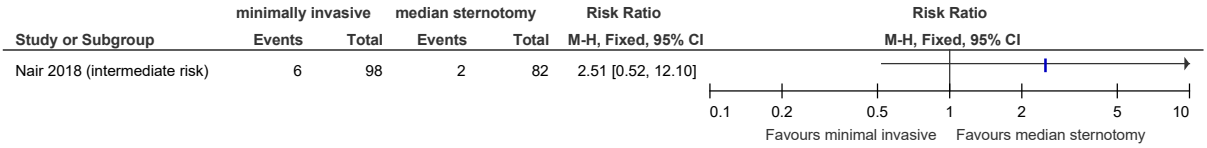
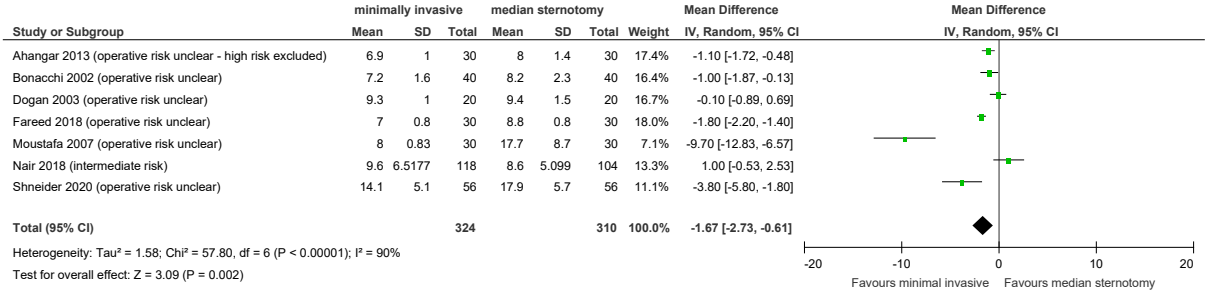
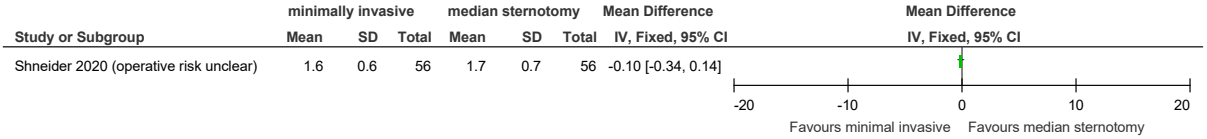


Figure 82: Length of hospital stay (final value) after intervention



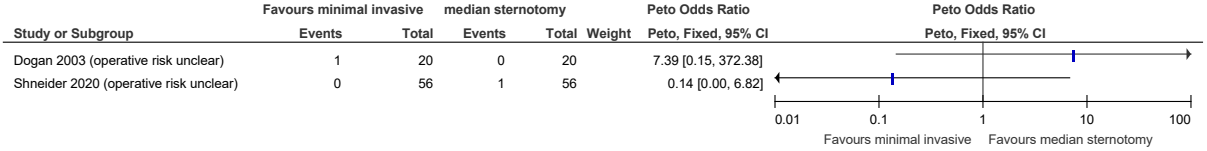
MIDs used to assess imprecision were calculated by multiplying the median SD in control groups across studies (2.3) by 0.5 and were ±1.15.

Figure 83: Length of intensive care unit stay (final value) after intervention



MIDs used to assess imprecision were calculated by multiplying the median SD in control groups across studies (0.7) by 0.5 and were ±0.35.

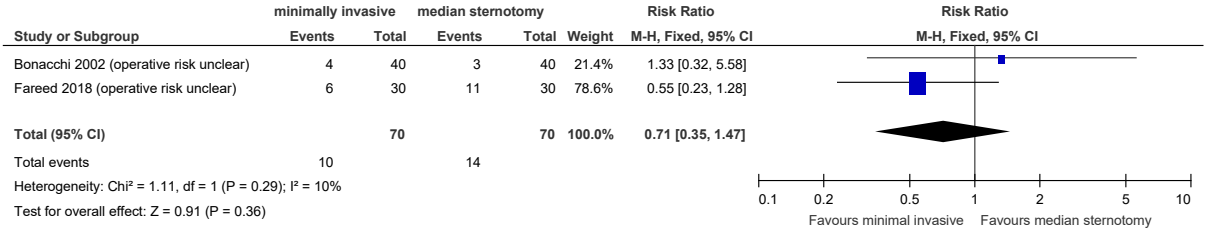
Figure 84: Intervention-related pacemaker implantation at 30 days (operative/postoperative)



Studies not pooled due to unexplained heterogeneity and random effects not being possible with Peto OR.

1

Figure 85: Intervention-related atrial fibrillation and postoperative arrhythmias during hospital admission

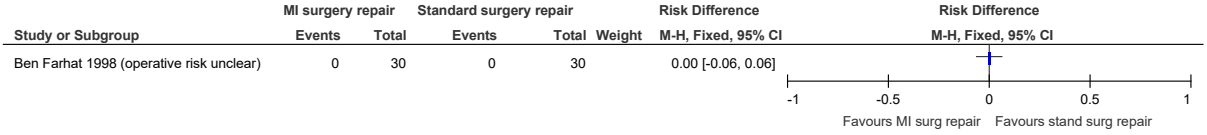


2

E.8 Mitral stenosis

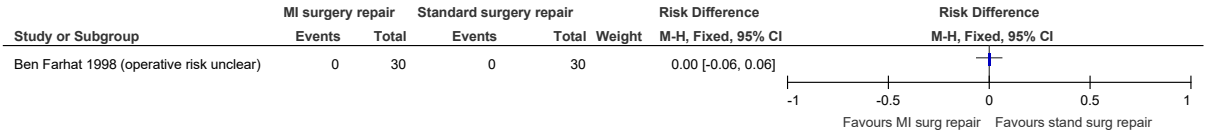
E.8.1 Minimally invasive surgery repair vs. standard surgery repair

Figure 86: All-cause mortality at ≥12 months (7 years)



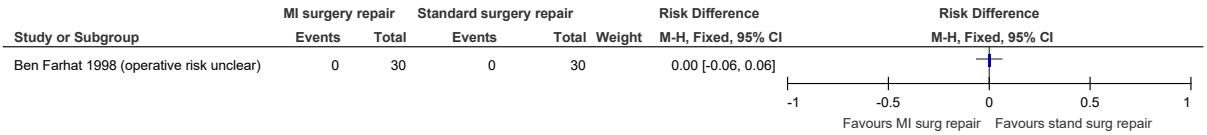
5

Figure 87: Cardiac mortality at ≥12 months (7 years)



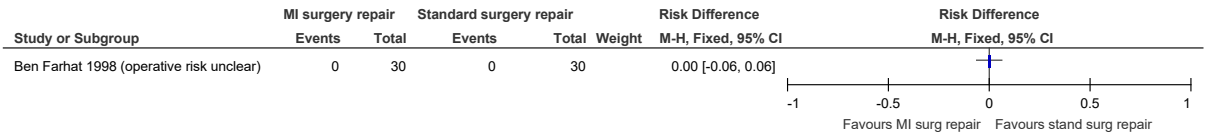
6

Figure 88: Intervention-related mortality at 30 days



7

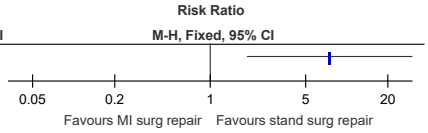
Figure 89: Intervention-related stroke or TIA at 30 days



1

Figure 90: Need for re-intervention at ≥12 months (7 years)

Study or Subgroup	MI surgery repair Events	Total	Standard surgery repair Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ben Farhat 1998 (operative risk unclear)	15	30	2	30		7.50 [1.88, 29.99]



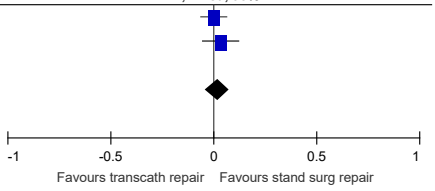
2

E.832 Transcatheter repair vs. standard surgery repair

Figure 91: All-cause mortality at ≥12 months (3-7 years)

Study or Subgroup	Transcatheter repair Events	Total	Standard surg repair Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Ben Farhat 1998 (operative risk unclear)	0	30	0	30	50.0%	0.00 [-0.06, 0.06]
Reyes 1994 (operative risk unclear)	1	30	0	30	50.0%	0.03 [-0.05, 0.12]
Total (95% CI)		**60**		**60**	**100.0%**	**0.02 [-0.04, 0.07]**
Total events	1		0			

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)

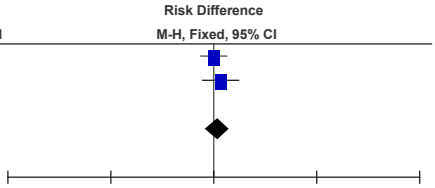


4

Figure 92: Cardiac mortality at ≥12 months (3-7 years)

Study or Subgroup	Transcatheter repair Events	Total	Standard surg repair Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Ben Farhat 1998 (operative risk unclear)	0	30	0	30	50.0%	0.00 [-0.06, 0.06]
Reyes 1994 (operative risk unclear)	1	30	0	30	50.0%	0.03 [-0.05, 0.12]
Total (95% CI)		**60**		**60**	**100.0%**	**0.02 [-0.04, 0.07]**
Total events	1		0			

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)

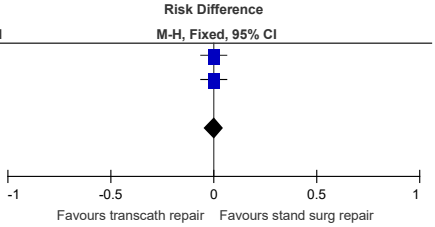


5

Figure 93: Intervention-related mortality at 30 days

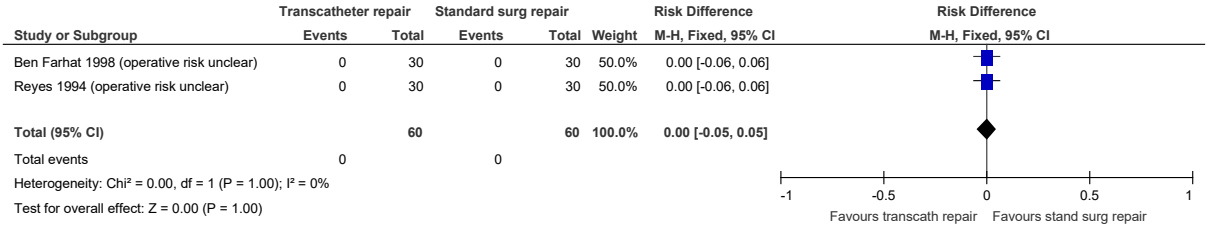
Study or Subgroup	Transcatheter repair Events	Total	Standard surg repair Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Ben Farhat 1998 (operative risk unclear)	0	30	0	30	50.0%	0.00 [-0.06, 0.06]
Reyes 1994 (operative risk unclear)	0	30	0	30	50.0%	0.00 [-0.06, 0.06]
Total (95% CI)		**60**		**60**	**100.0%**	**0.00 [-0.05, 0.05]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)



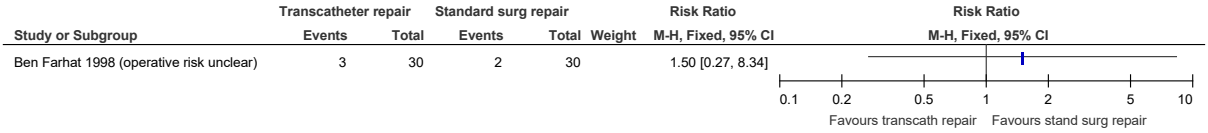
6

Figure 94: Intervention-related stroke or TIA at 30 days



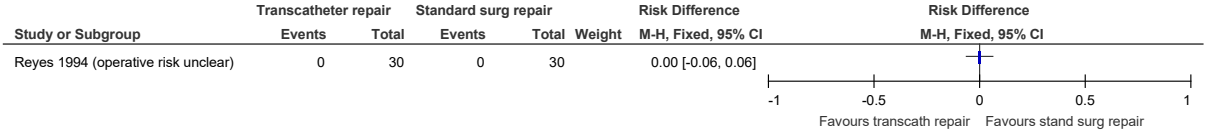
1

Figure 95: Need for re-intervention at ≥12 months (7 years)



2

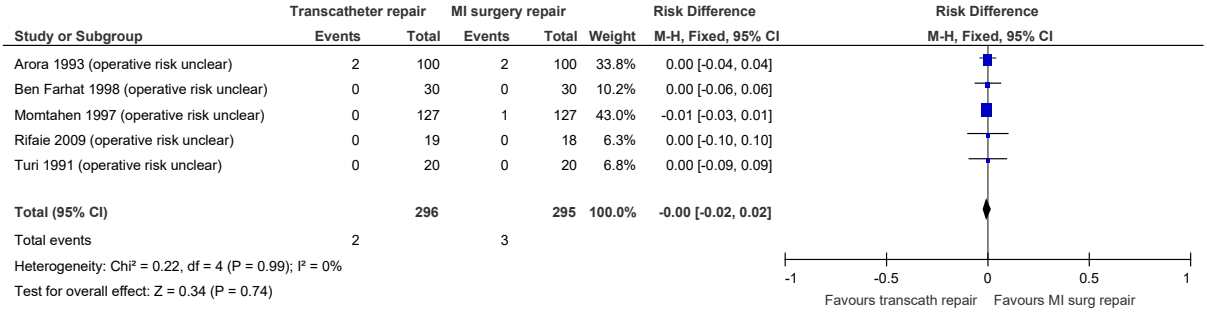
Figure 96: Intervention-related atrial fibrillation at 30 days



3

E.8.3 Transcatheter repair vs. minimally invasive surgery repair

Figure 97: All-cause mortality at ≥12 months (unclear – 8 years)

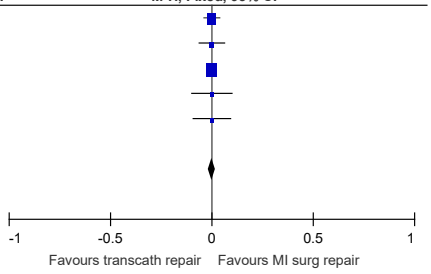


5

Figure 98: Cardiac mortality at ≥12 months (unclear – 8 years)

Study or Subgroup	Transcatheter repair Events	Total	MI surgery repair Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Arora 1993 (operative risk unclear)	2	100	2	100	33.8%	0.00 [-0.04, 0.04]
Ben Farhat 1998 (operative risk unclear)	0	30	0	30	10.2%	0.00 [-0.06, 0.06]
Momtahen 1997 (operative risk unclear)	0	127	0	127	43.0%	0.00 [-0.02, 0.02]
Rifaie 2009 (operative risk unclear)	0	19	0	18	6.3%	0.00 [-0.10, 0.10]
Turi 1991 (operative risk unclear)	0	20	0	20	6.8%	0.00 [-0.09, 0.09]
Total (95% CI)		**296**		**295**	**100.0%**	**0.00 [-0.02, 0.02]**
Total events	2		2			

Heterogeneity: Chi² = 0.00, df = 4 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

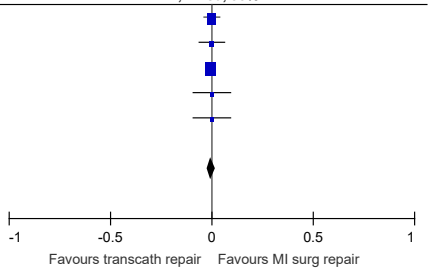


1

Figure 99: Intervention-related mortality at 30 days

Study or Subgroup	Transcatheter repair Events	Total	MI surgery repair Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Arora 1993 (operative risk unclear)	2	100	2	100	33.7%	0.00 [-0.04, 0.04]
Ben Farhat 1998 (operative risk unclear)	0	30	0	30	10.1%	0.00 [-0.06, 0.06]
Momtahen 1997 (operative risk unclear)	0	127	1	127	42.8%	-0.01 [-0.03, 0.01]
Rifaie 2009 (operative risk unclear)	0	20	0	20	6.7%	0.00 [-0.09, 0.09]
Turi 1991 (operative risk unclear)	0	20	0	20	6.7%	0.00 [-0.09, 0.09]
Total (95% CI)		**297**		**297**	**100.0%**	**-0.00 [-0.02, 0.02]**
Total events	2		3			

Heterogeneity: Chi² = 0.22, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.74)

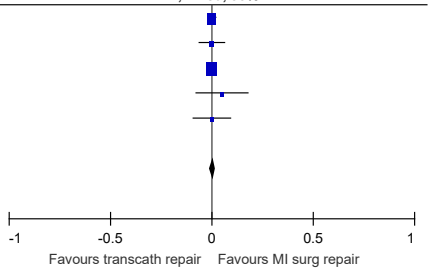


2

Figure 100: Intervention-related stroke or TIA at 30 days

Study or Subgroup	Transcatheter repair Events	Total	MI surgery repair Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Arora 1993 (operative risk unclear)	0	98	0	98	33.2%	0.00 [-0.02, 0.02]
Ben Farhat 1998 (operative risk unclear)	0	30	0	30	10.2%	0.00 [-0.06, 0.06]
Momtahen 1997 (operative risk unclear)	0	127	0	127	43.1%	0.00 [-0.02, 0.02]
Rifaie 2009 (operative risk unclear)	1	20	0	20	6.8%	0.05 [-0.08, 0.18]
Turi 1991 (operative risk unclear)	0	20	0	20	6.8%	0.00 [-0.09, 0.09]
Total (95% CI)		**295**		**295**	**100.0%**	**0.00 [-0.01, 0.02]**
Total events	1		0			

Heterogeneity: Chi² = 0.83, df = 4 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)

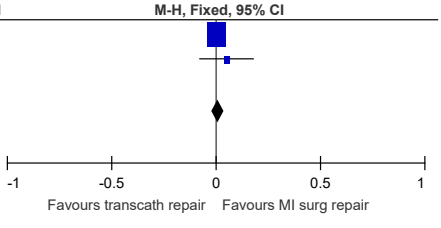


3

Figure 101: Intervention-related major bleeding at 30 days

Study or Subgroup	Transcatheter repair Events	Total	MI surgery repair Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Arora 1993 (operative risk unclear)	0	98	0	98	83.1%	0.00 [-0.02, 0.02]
Turi 1991 (operative risk unclear)	1	20	0	20	16.9%	0.05 [-0.08, 0.18]
Total (95% CI)		**118**		**118**	**100.0%**	**0.01 [-0.02, 0.04]**
Total events	1		0			

Heterogeneity: Chi² = 1.11, df = 1 (P = 0.29); I² = 10%
Test for overall effect: Z = 0.59 (P = 0.56)

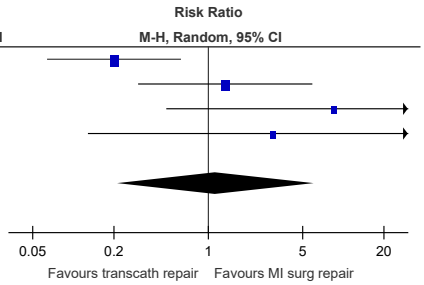


1

Figure 102: Need for re-intervention at ≥12 months (unclear – 8 years)

Study or Subgroup	Transcatheter repair Events	Total	MI surgery repair Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ben Farhat 1998 (operative risk unclear)	3	30	15	30	34.1%	0.20 [0.06, 0.62]
Momtahen 1997 (operative risk unclear)	4	127	3	127	30.7%	1.33 [0.30, 5.84]
Rifaie 2009 (operative risk unclear)	4	19	0	18	18.6%	8.55 [0.49, 148.33]
Turi 1991 (operative risk unclear)	1	20	0	20	16.7%	3.00 [0.13, 69.52]
Total (95% CI)		**196**		**195**	**100.0%**	**1.13 [0.21, 6.03]**
Total events	12		18			

Heterogeneity: Tau² = 1.81; Chi² = 9.17, df = 3 (P = 0.03); I² = 67%
Test for overall effect: Z = 0.14 (P = 0.89)

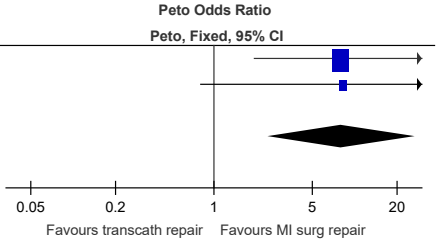


2

Figure 103: Major vascular complications at 30 days

Study or Subgroup	Transcatheter repair Events	Total	MI surgery repair Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arora 1993 (operative risk unclear)	8	100	0	100	73.1%	7.95 [1.94, 32.59]
Turi 1991 (operative risk unclear)	3	20	0	20	26.9%	8.23 [0.81, 84.07]
Total (95% CI)		**120**		**120**	**100.0%**	**8.02 [2.40, 26.80]**
Total events	11		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 3.38 (P = 0.0007)

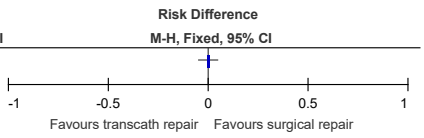


3

E.8.4 Transcatheter repair vs. surgical repair (unclear/mixed invasiveness)

Figure 104: All-cause mortality at ≥12 months (2 years)

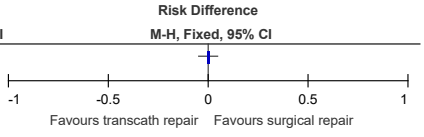
Study or Subgroup	Transcatheter repair Events	Total	Surgical repair (mix inv) Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Cardoso 2002 (operative risk unclear)	0	40	0	40		0.00 [-0.05, 0.05]



5

Figure 105: Cardiac mortality at ≥12 months (2 years)

Study or Subgroup	Transcatheter repair Events	Total	Surgical repair (mix inv) Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Cardoso 2002 (operative risk unclear)	0	40	0	40		0.00 [-0.05, 0.05]



6

Figure 106: Intervention-related mortality at 30 days

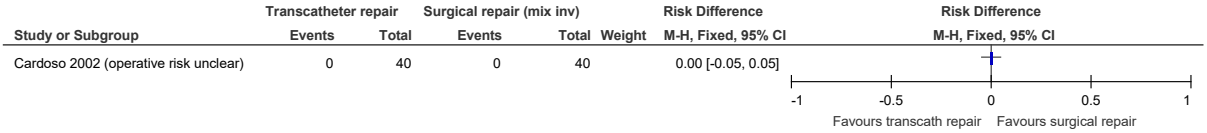


Figure 107: Intervention-related major bleeding at 30 days (postoperative)

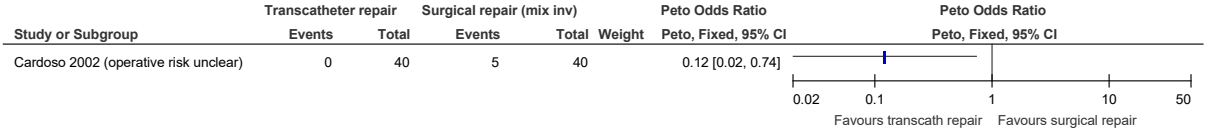


Figure 108: Need for re-intervention at ≥12 months (2 years)

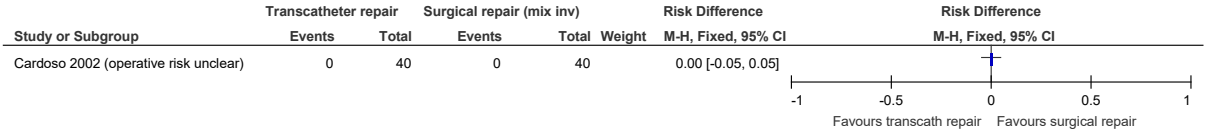


Figure 109: Intervention-related pacemaker implantation at 30 days (postoperative)

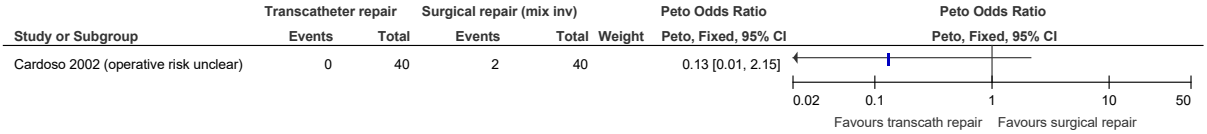


Figure 110: Intervention-related atrial fibrillation at 30 days (postoperative)

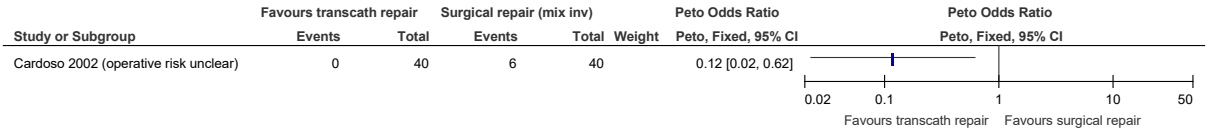
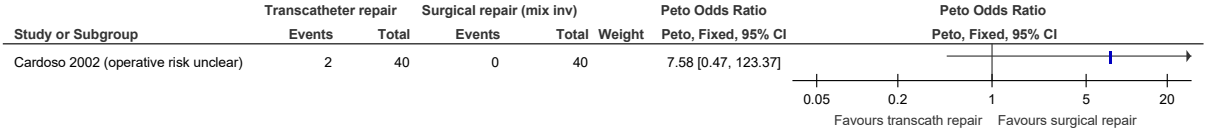


Figure 111: Major vascular complications at 30 days (postoperative)



E.9 Mitral regurgitation

E.9.1 Standard surgery replacement vs. standard surgery repair

Figure 112: Cardiac mortality at ≥12 months (in-hospital)

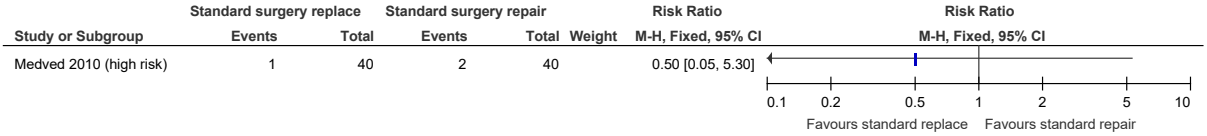


Figure 113: Intervention-related mortality at 30 days (in-hospital)

Figure 114: Intervention-related stroke or TIA at 30 days (in-hospital)

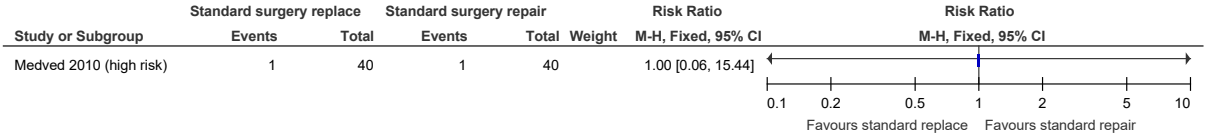


Figure 115: Need for re-intervention at ≥12 months (in-hospital)

E.9.12 Minimally invasive surgery repair vs. standard surgery repair

Figure 116: All-cause mortality at ≥12 months (3 years)

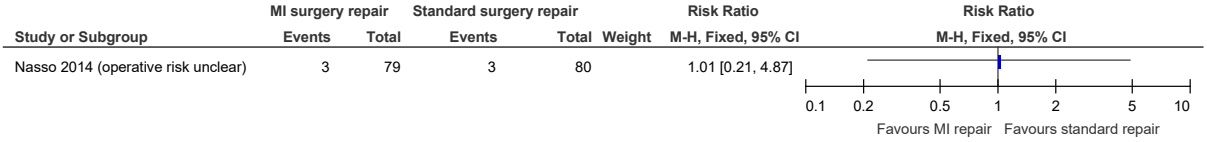


Figure 117: Intervention-related mortality at 30 days (intraoperative/early postoperative period)

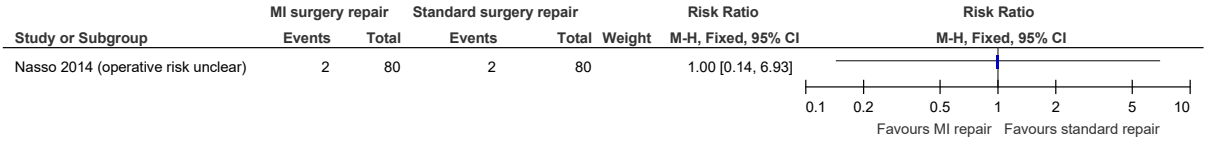
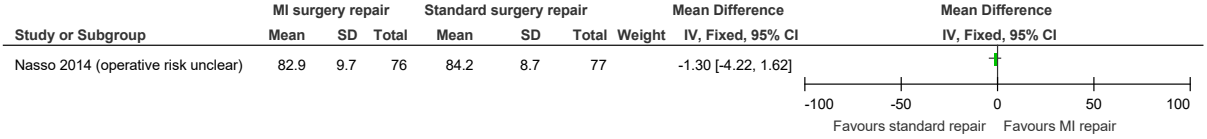
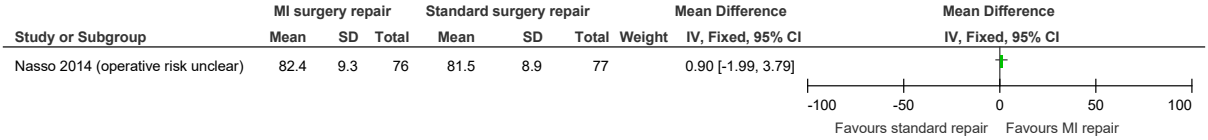


Figure 118: Quality of life at ≥12 months (3 years) – SF-36 general health domain



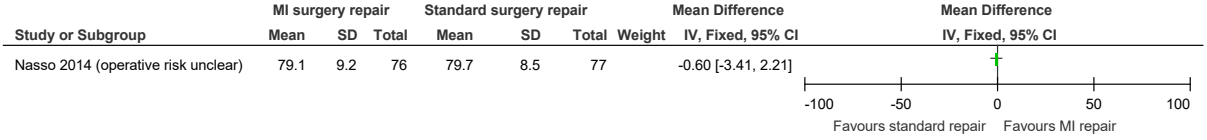
Published MIDs of ±2.00 for the general health domain of the SF-36 questionnaire were used to assessed imprecision.

Figure 119: Quality of life at ≥12 months (3 years) – SF-36 mental health domain



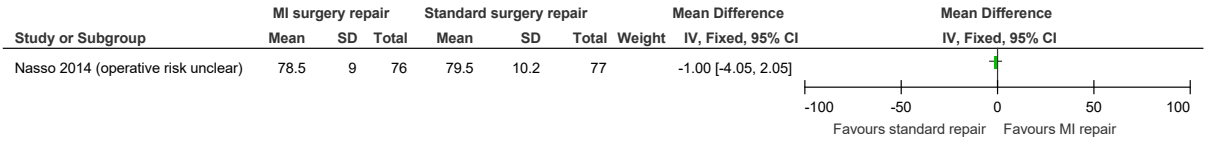
Published MIDs of ±3.00 for the mental health domain of the SF-36 questionnaire were used to assessed imprecision.

Figure 120: Quality of life at ≥12 months (3 years) – SF-36 physical activity domain



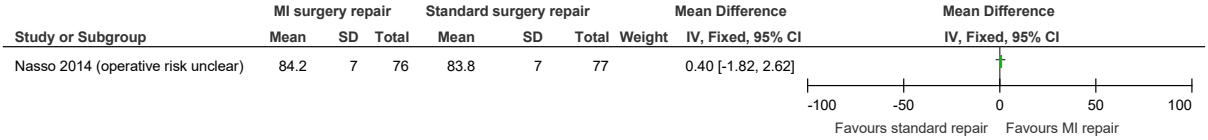
Published MIDs of ±3.00 for the physical activity (physical functioning?) domain of the SF-36 questionnaire were used to assessed imprecision.

Figure 121: Quality of life at ≥12 months (3 years) – SF-36 role limitation domain



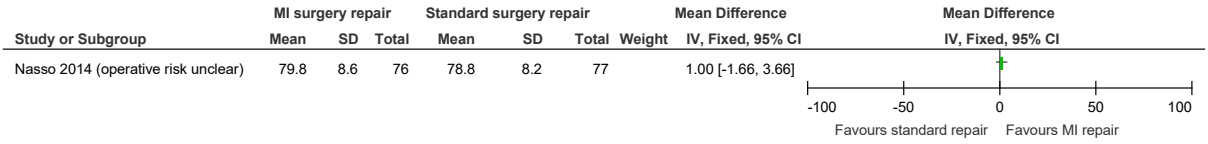
Published MIDs of ±3.00 for the role limitation (role-physical?) domain of the SF-36 questionnaire were used to assessed imprecision.

Figure 122: Quality of life at ≥12 months (3 years) – SF-36 social activities domain



Published MIDs of ±3.00 for the social activities (social functioning?) domain of the SF-36 questionnaire were used to assessed imprecision.

Figure 123: Quality of life at ≥12 months (3 years) – SF-36 vitality domain



Published MIDs of ±2.00 for the vitality domain of the SF-36 questionnaire were used to assessed imprecision.

Figure 124: Intervention-related stroke or TIA at 30 days (intra/early postoperative period)

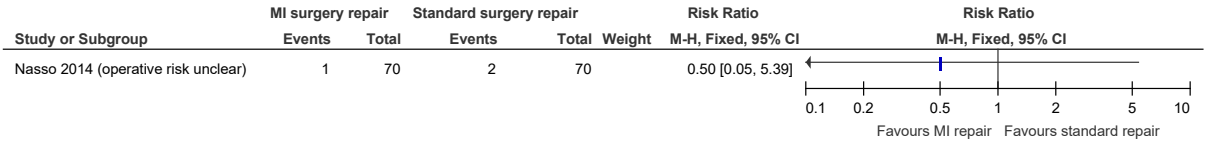
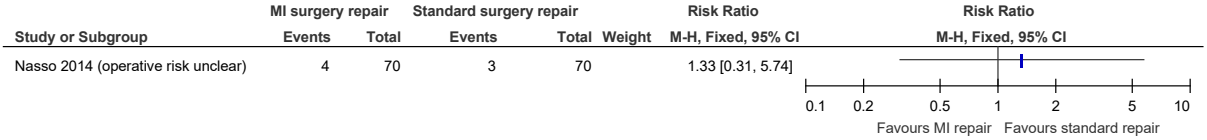
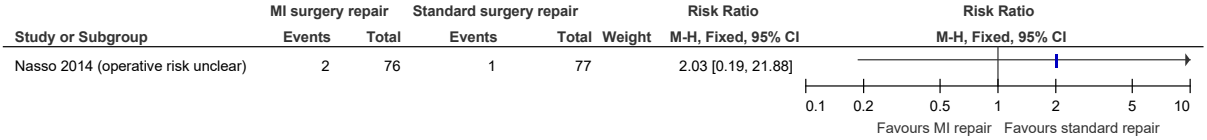


Figure 125: Intervention-related major bleeding at 30 days (intra/early postoperative period)



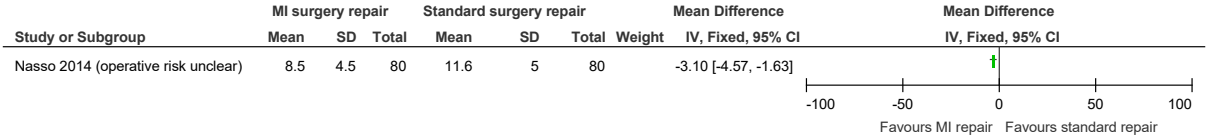
1

Figure 126: Need for re-intervention at ≥12 months (3 years)



2

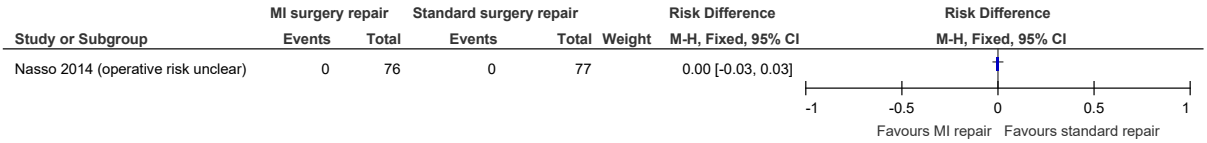
Figure 127: Length of hospital stay post-intervention



MIDs used to assess imprecision were calculated by multiplying the median SD in control groups across studies (5.0) by 0.5 and were ±2.50.

3

Figure 128: Prosthetic valve endocarditis at ≥12 months (3 years)



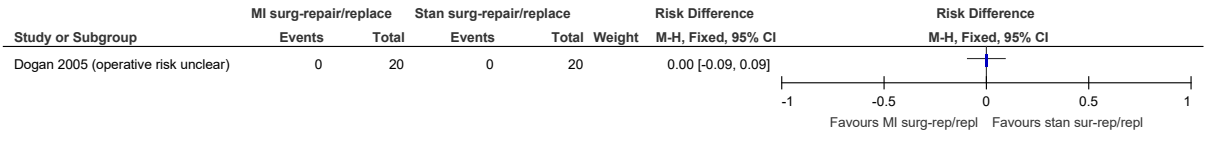
4

E.953 Minimally invasive surgery (mixed repair/replace) vs. standard surgery (mixed repair/replace)

6

7

Figure 129: Cardiac mortality at ≥12 months (in-hospital)

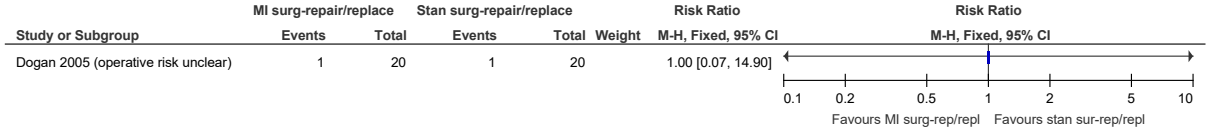


1

Figure 130: Intervention-related mortality at 30 days (in-hospital)

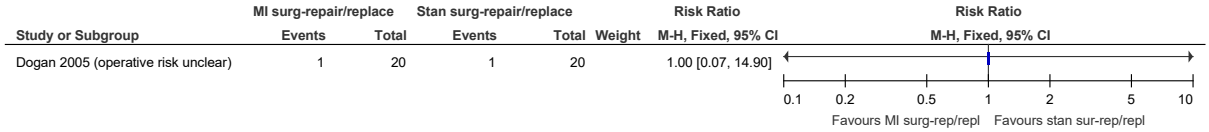
2

Figure 131: Onset or exacerbation of heart failure at ≥12 months (postoperative)



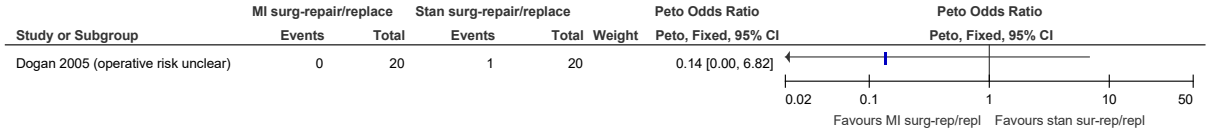
3

Figure 132: Intervention-related stroke or TIA at 30 days (postoperative)



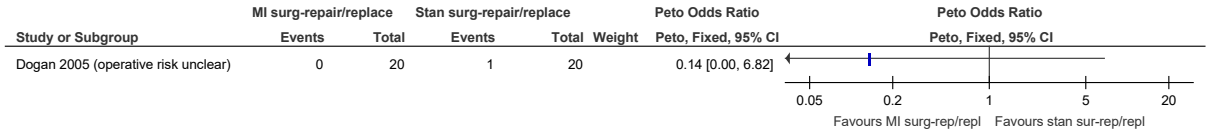
4

Figure 133: Intervention-related major bleeding at 30 days (postoperative)



5

Figure 134: Intervention-related pacemaker implantation at 30 days (postoperative)



6

E.9.14 Surgical replacement (unclear/mixed invasiveness) vs. surgical repair (unclear/mixed invasiveness)

Figure 135: All-cause mortality at ≥12 months (2 years) – time-to-event data

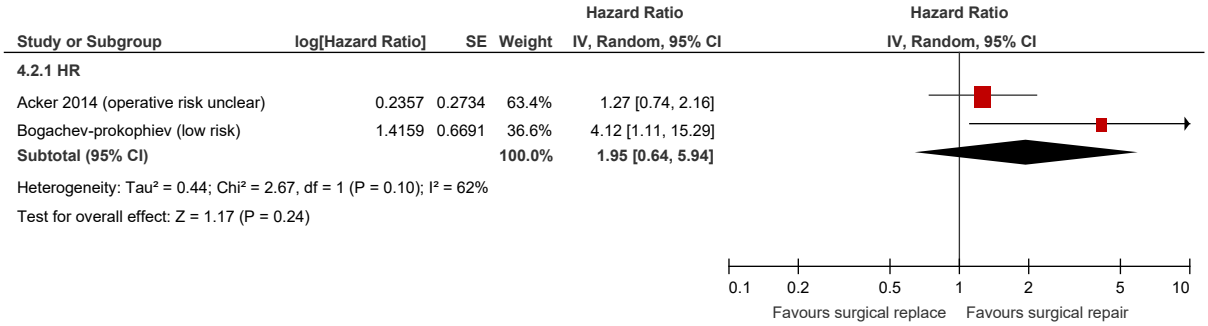


Figure 136: Cardiac mortality at ≥12 months (24 months)

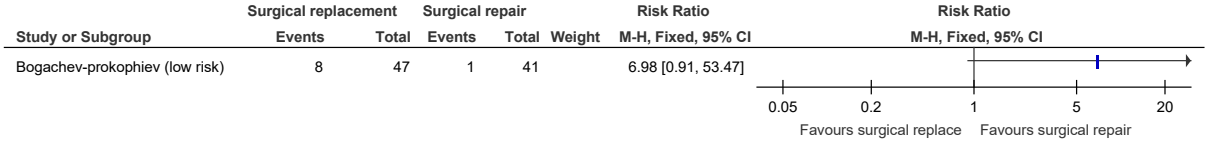


Figure 137: Intervention-related mortality at 30 days

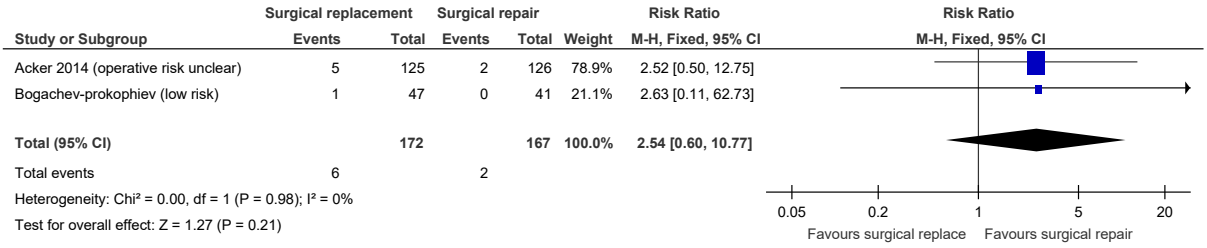
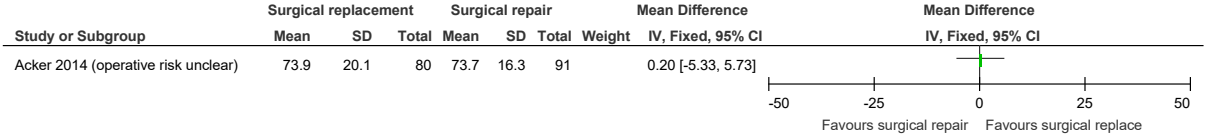
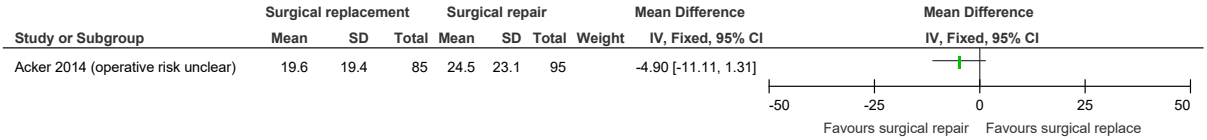


Figure 138: Quality of life at ≥12 months (12 months) – EQ-5D, 0-100 scale



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (23.95) by 0.5 and were ±11.98.

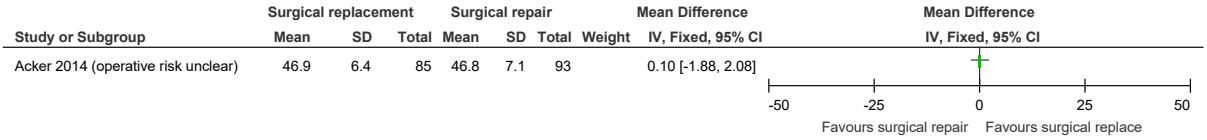
Figure 139: Quality of life at ≥12 months (12 months) – Minnesota Living with Heart Failure Questionnaire



1 Published MIDs of ±5.0 for the MLWHF questionnaire were used to assessed imprecision

2

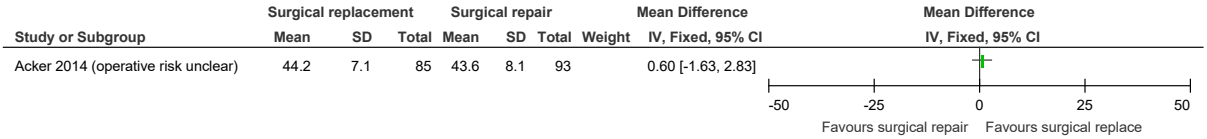
Figure 140: Quality of life at ≥12 months (12 months) – SF-12 mental function



3 MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (8.4)
4 by 0.5 and were ±4.2.

5

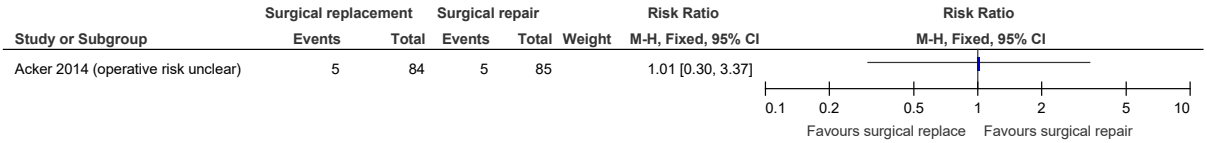
Figure 141: Quality of life at ≥12 months (12 months) – SF-12 physical function



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (7.65) by 0.5 and were ±3.83.

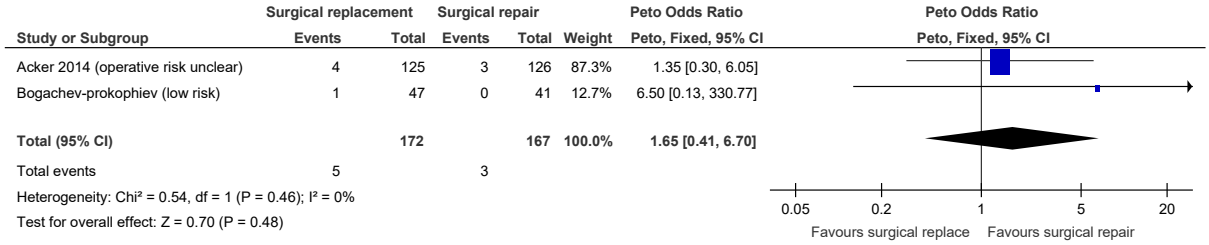
6

Figure 142: Onset or exacerbation of heart failure at ≥12 months (2 years)



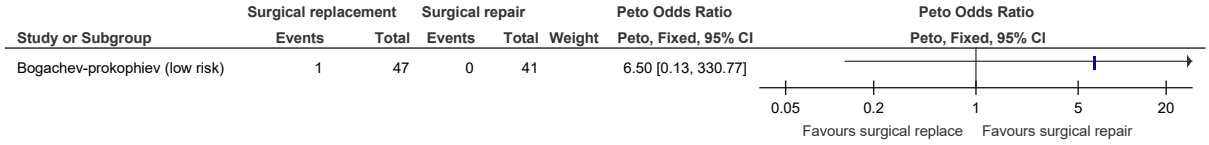
7

Figure 143: Intervention-related stroke or TIA at 30 days



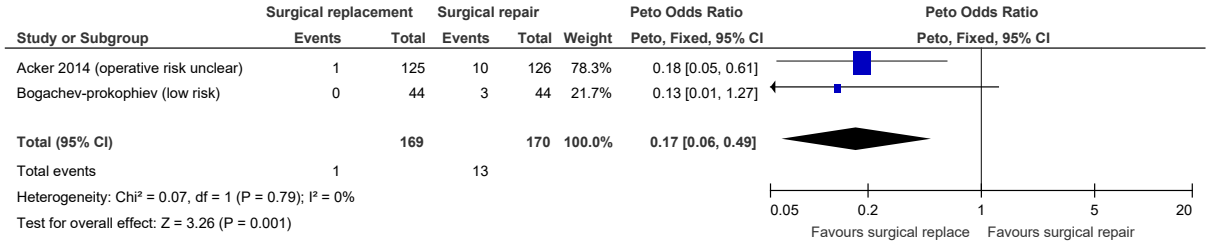
1

Figure 144: Intervention-related major bleeding at 30 days (postoperative)



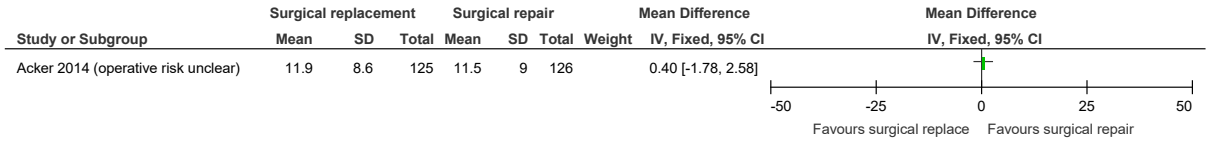
2

Figure 145: Need for re-intervention at ≥12 months (2 years)



3

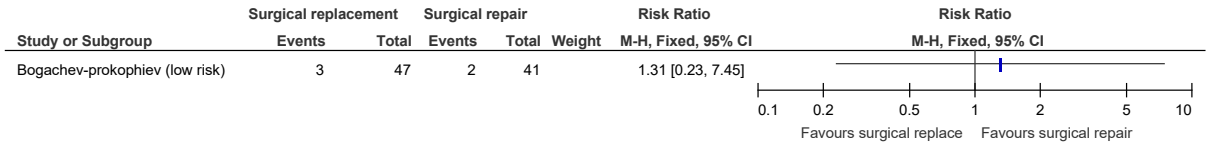
Figure 146: Length of stay post-intervention



MIDs used to assess imprecision were calculated by multiplying the median SD in control groups across studies (9.0) by 0.5 and were ±4.50.

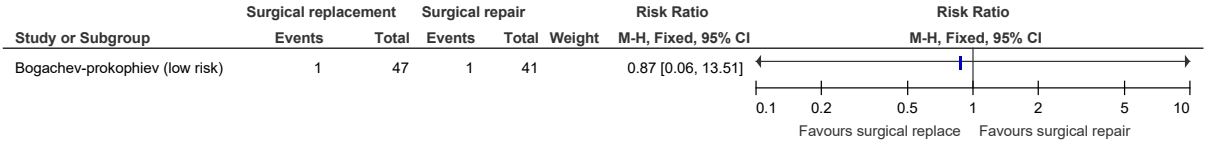
4

Figure 147: Intervention-related pacemaker implantation at 30 days (postoperative)



1

Figure 148: Major vascular complications at 30 days (intraoperative)



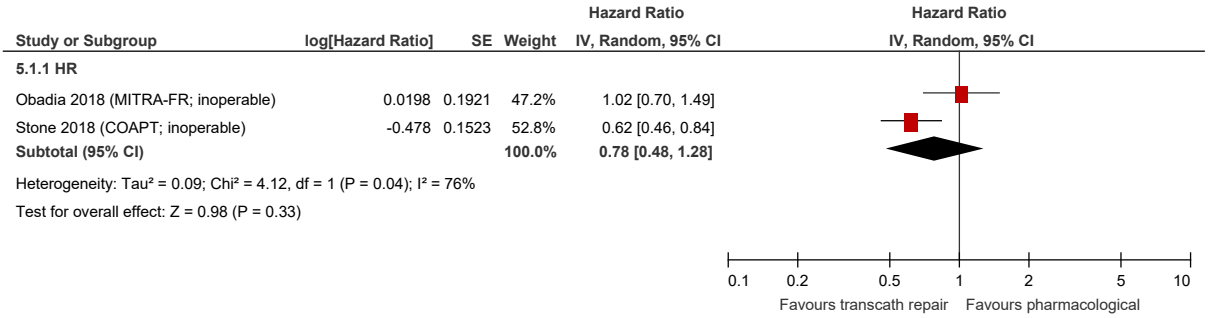
2

Figure 149: Prosthetic valve endocarditis at ≥12 months (2 years)

3

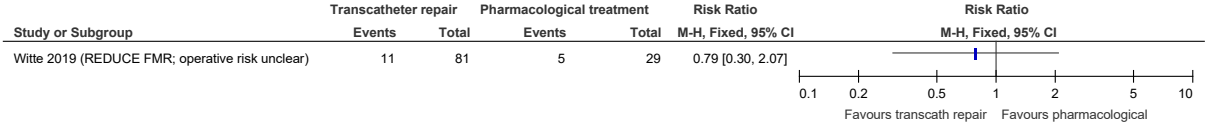
E.9.5 Transcatheter repair vs. pharmacological management

Figure 150: All-cause mortality at ≥12 months (24 months) - time-to-event data



5

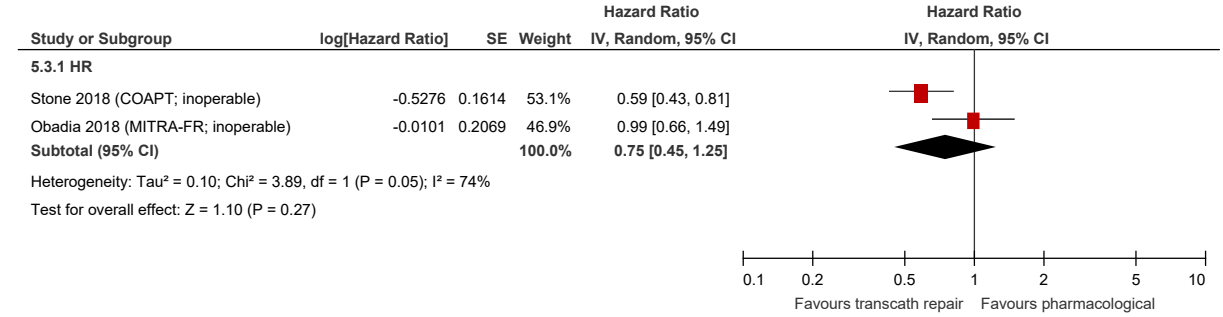
Figure 151: All-cause mortality at ≥12 months (12 months) – dichotomous data



6

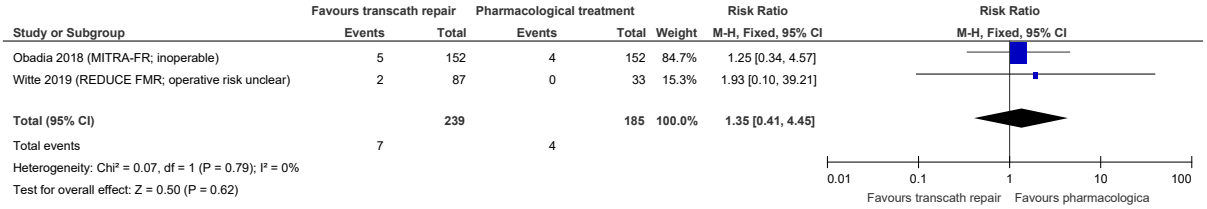
7

Figure 152: Cardiac mortality at ≥12 months (24 months) - time-to-event data



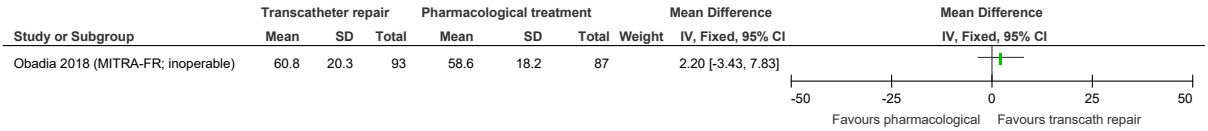
1

Figure 153: Intervention-related mortality at 30 days



2

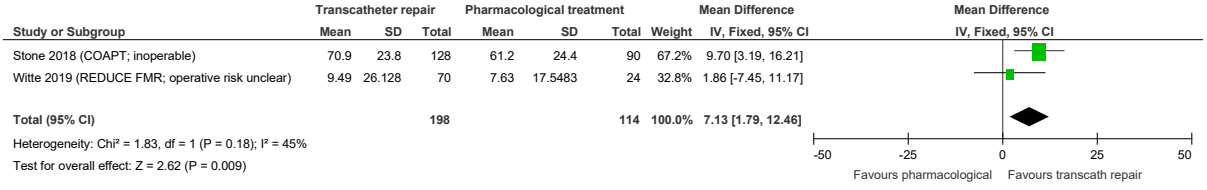
Figure 154: Quality of life (EQ-5D) at ≥12 months (12 months)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (17.90 by 0.5 and were ±8.95.

3

Figure 155: Quality of life (KCCQ overall) at ≥12 months (12-24 months)

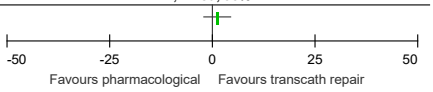


MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (23.05) by 0.5 and were ±11.53.

4

Figure 156: Quality of life (SF-36 mental component) at ≥12 months (24 months)

Study or Subgroup	Transcatheter repair Mean	SD	Total	Pharmacological treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Stone 2018 (COAPT; inoperable)	50.1	12.6	127	48.9	11.7	90		1.20 [-2.06, 4.46]

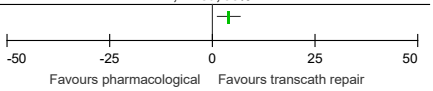


Published MIDs of ±3.0 for the SF-36 mental component score were used to assessed imprecision.

1

Figure 157: Quality of life (SF-36 physical component) at ≥12 months (24 months)

Study or Subgroup	Transcatheter repair Mean	SD	Total	Pharmacological treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Stone 2018 (COAPT; inoperable)	38.1	10.2	127	34.1	10.2	90		4.00 [1.25, 6.75]



Published MIDs of ±2.0 for the SF-36 physical component score were used to assessed imprecision.

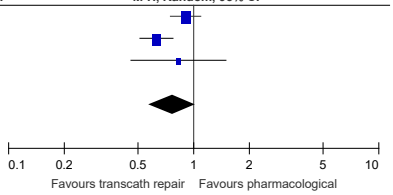
2

Figure 158: Onset or exacerbation of heart failure at ≥12 months (12-24 months)

Study or Subgroup	Transcatheter repair Events	Total	Pharmacological treatment Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Obadia 2018 (MITRA-FR; inoperable)	85	152	94	152	42.5%	0.90 [0.75, 1.09]
Stone 2018 (COAPT; inoperable)	92	302	151	312	41.1%	0.63 [0.51, 0.77]
Witte 2019 (REDUCE FMR; operative risk unclear)	24	87	11	33	16.4%	0.83 [0.46, 1.49]
Total (95% CI)		**541**		**497**	**100.0%**	**0.77 [0.57, 1.03]**
Total events	201		256			

Heterogeneity: Tau² = 0.04; Chi² = 6.84, df = 2 (P = 0.03); I² = 71%

Test for overall effect: Z = 1.79 (P = 0.07)



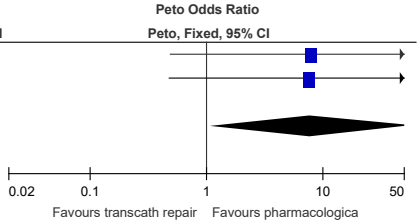
3

Figure 159: Intervention-related stroke or TIA at 30 days (periprocedural – 30 days)

Study or Subgroup	Transcatheter repair Events	Total	Pharmacological treatment Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Obadia 2018 (MITRA-FR; inoperable)	2	144	0	152	49.9%	7.87 [0.49, 126.48]
Stone 2018 (COAPT; inoperable)	2	302	0	312	50.1%	7.66 [0.48, 122.84]
Total (95% CI)		**446**		**464**	**100.0%**	**7.76 [1.09, 55.28]**
Total events	4		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%

Test for overall effect: Z = 2.05 (P = 0.04)



4

Figure 160: Intervention-related major bleeding at 30 days (periprocedural)

Study or Subgroup	Transcatheter repair Events	Total	Pharmacological treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Obadia 2018 (MITRA-FR; inoperable)	11	152	6	152		1.83 [0.70, 4.83]

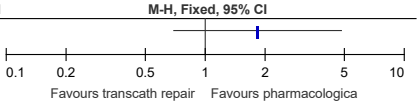


Figure 161: Need for re-intervention at ≥12 months (24 months) - time-to-event data

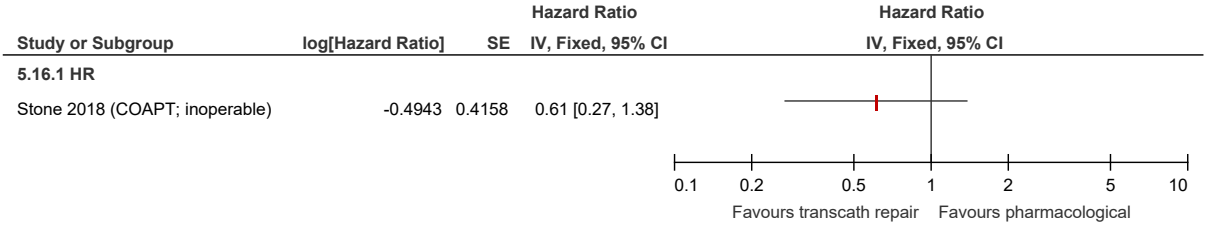
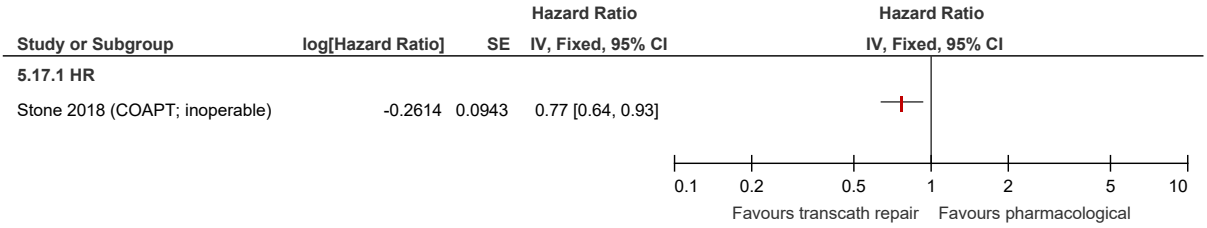
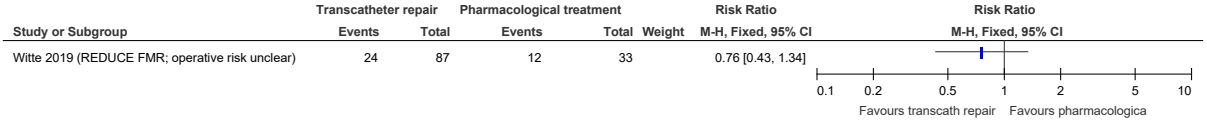


Figure 162: Rehospitalisation at ≥12 months (24 months) - time-to-event data



1

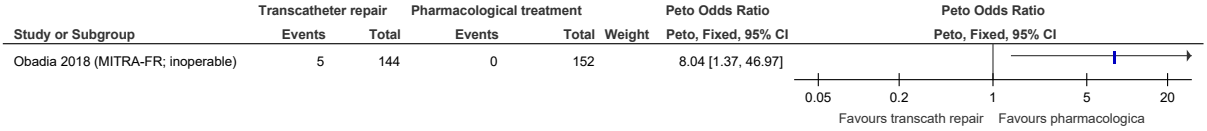
Figure 163: Rehospitalisation for heart failure at ≥12 months (12 months) - dichotomous data



2

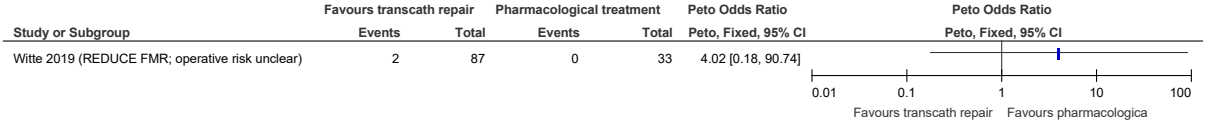
3

Figure 164: Major vascular complications at 30 days (periprocedural)



4

Figure 165: Endocarditis at ≥12 months (12 months)



E.926 Transcatheter repair vs. surgery (mixed repair/replacement and unclear/mixed invasiveness)

Figure 166: All-cause mortality at ≥12 months (5 years)

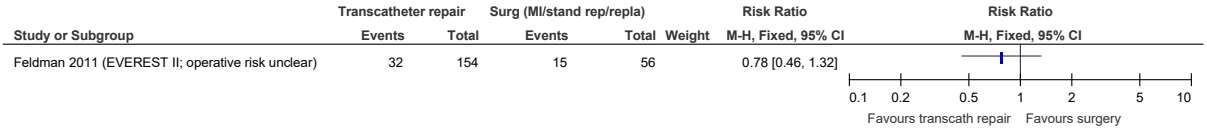


Figure 167: Intervention-related mortality at 30 days

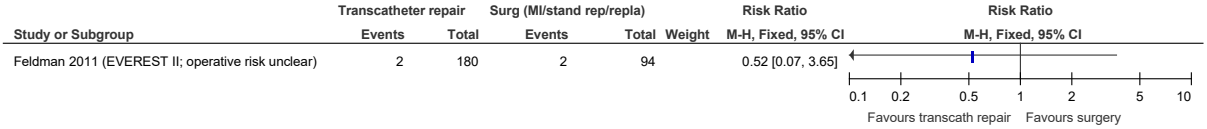
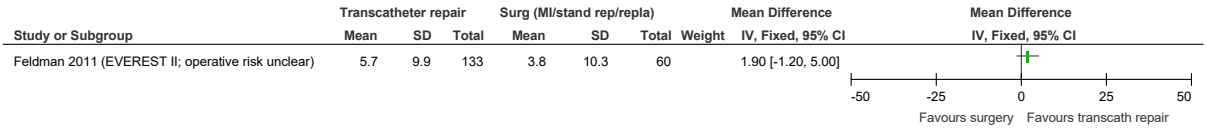
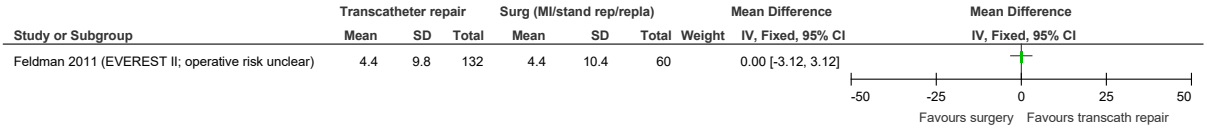


Figure 168: Quality of life (SF-36 mental component) at ≥12 months (12 months) - change scores



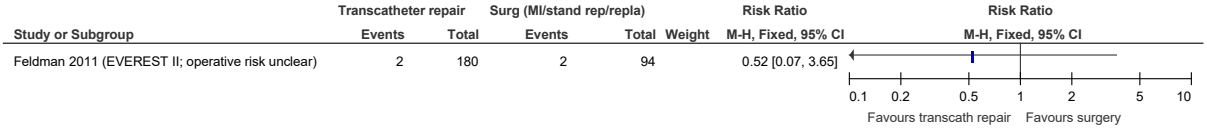
Published MIDs of ±3.0 for the SF-36 mental component score were used to assessed imprecision.

Figure 169: Quality of life (SF-36 physical component) at ≥12 months (12 months) - change scores



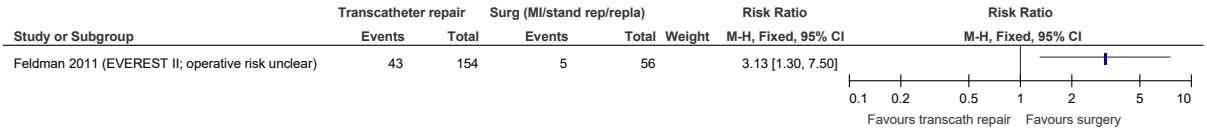
Published MIDs of ±2.0 for the SF-36 physical component score were used to assessed imprecision.

Figure 170: Intervention-related stroke or TIA at 30 days



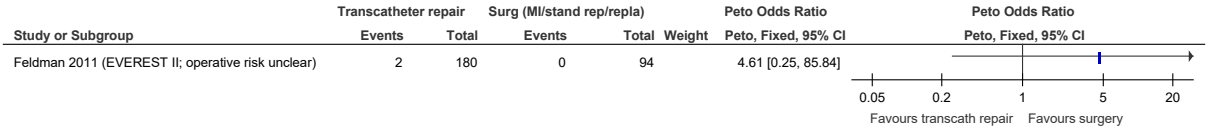
1

Figure 171: Need for re-intervention at ≥12 months (5 years)



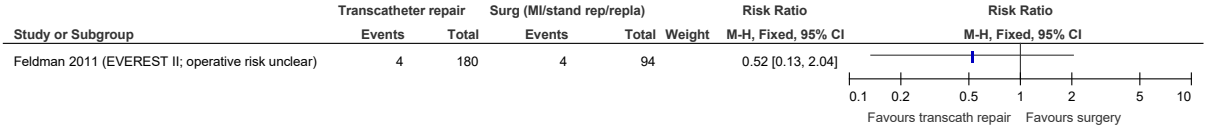
2

Figure 172: Intervention-related atrial fibrillation at 30 days



3

Figure 173: Major vascular complications at 30 days



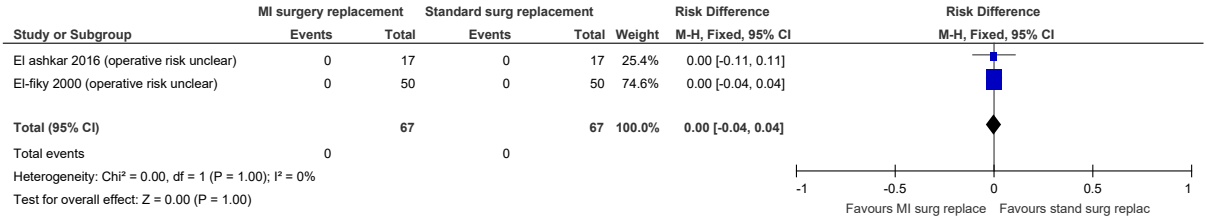
4

E.10 Unclear/mixed mitral valve disease

E.10.1 Minimally invasive surgery replacement vs. standard surgery replacement

7

Figure 174: Cardiac mortality at ≥12 months (in-hospital/postoperative)

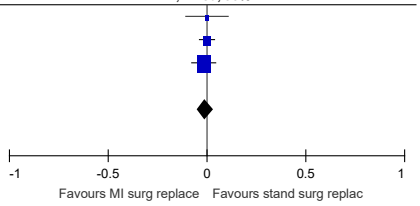


1

Figure 175: Intervention-related mortality at 30 days (in-hospital/postoperative)

Study or Subgroup	MI surgery replacement Events	Total	Standard surg replacement Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
El ashkar 2016 (operative risk unclear)	0	17	0	17	9.5%	0.00 [-0.11, 0.11]
El-fiky 2000 (operative risk unclear)	0	50	0	50	28.0%	0.00 [-0.04, 0.04]
Malik 2015 (operative risk unclear)	4	77	14	204	62.5%	-0.02 [-0.08, 0.04]
Total (95% CI)		**144**		**271**	**100.0%**	**-0.01 [-0.05, 0.03]**
Total events	4		14			

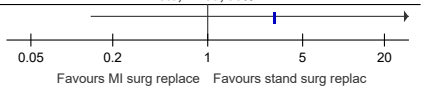
Heterogeneity: Chi² = 0.36, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)



2

Figure 176: Intervention-related stroke or TIA at 30 days (reported as CVA with no definition – assumed to be cerebrovascular accident)

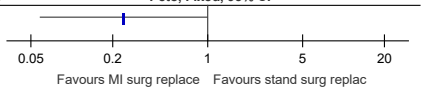
Study or Subgroup	MI surgery replacement Events	Total	Standard surg replacement Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Malik 2015 (operative risk unclear)	1	77	1	204		3.13 [0.14, 70.31]



3

Figure 177: Need for re-intervention at ≥12 months (postoperative, defined as re-opening)

Study or Subgroup	MI surgery replacement Events	Total	Standard surg replacement Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Malik 2015 (operative risk unclear)	0	77	10	204		0.24 [0.06, 0.99]

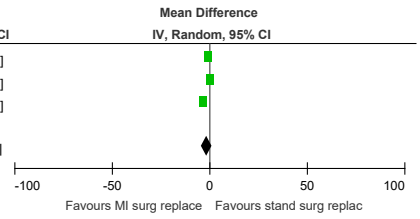


4

Figure 178: Length of stay post-intervention

Study or Subgroup	MI surgery replacement Mean	SD	Total	Standard surg replacement Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
El ashkar 2016 (operative risk unclear)	3	1.78	17	3.72	1.9	17	32.1%	-0.72 [-1.96, 0.52]
El-fiky 2000 (operative risk unclear)	7	2	50	7	2	50	33.5%	0.00 [-0.78, 0.78]
Malik 2015 (operative risk unclear)	5	0.5	77	8.5	0.5	204	34.5%	-3.50 [-3.63, -3.37]
Total (95% CI)			**144**			**271**	**100.0%**	**-1.44 [-4.09, 1.22]**

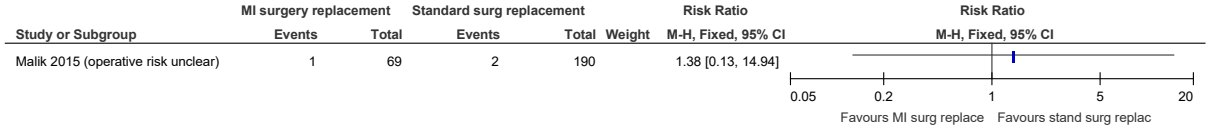
Heterogeneity: Tau² = 5.32; Chi² = 92.36, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.06 (P = 0.29)



5 MIDs used to assess imprecision were calculated by multiplying the median SD in control groups across studies
6 (1.9) by 0.5 and were ±0.95.

7

Figure 179: Prosthetic valve endocarditis at 12 months (2 years)



1

E.11 Tricuspid regurgitation

E.11.1 Transcatheter repair + medical vs. medical alone

4

Figure 180: All-cause mortality at ≥12 months (12 months)

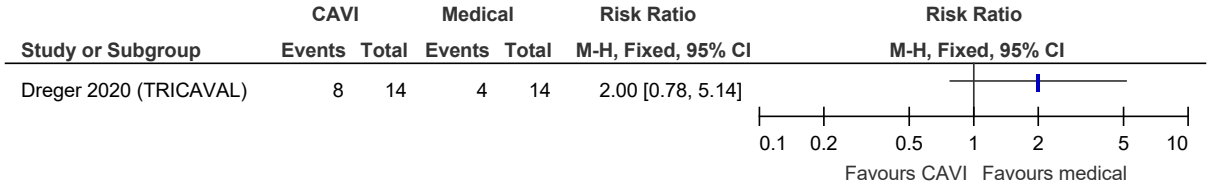


Figure 181: Cardiac mortality (right heart failure) at ≥12 months (12 months)

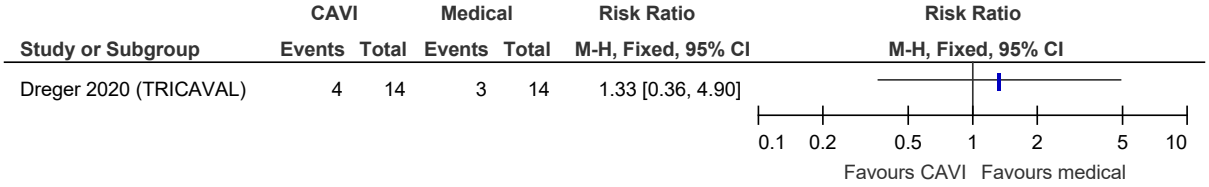


Figure 182: Intervention-related mortality at 30 days (in-hospital)

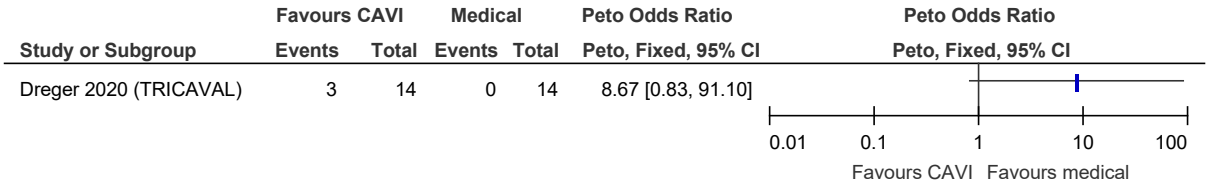
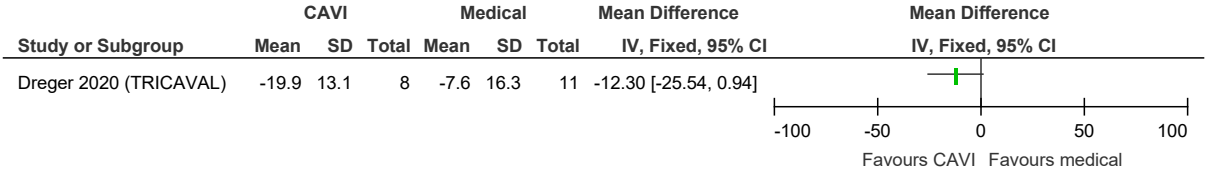


Figure 183: Quality of life (MLWHF questionnaire, change from baseline) at ≥12 months (3 months)



Published MIDs of ±5.0 for the MLWHF questionnaire were used to assessed imprecision

Figure 184: Onset or exacerbation of heart failure (NYHA class worsening by 1 or 2 classes) at ≥12 months (3 months)

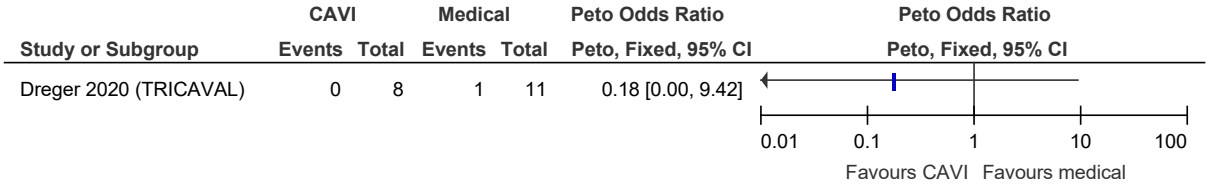


Figure 185: Intervention-related major bleeding (haemorrhage) at 30 days

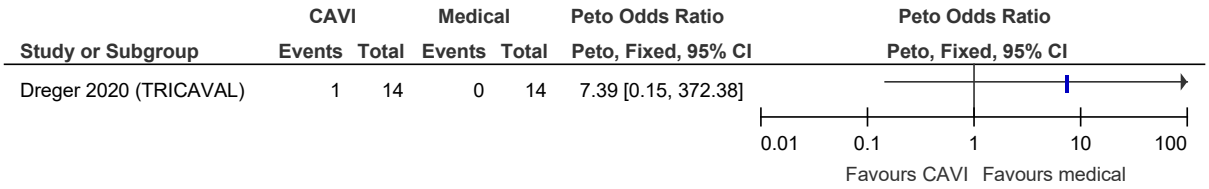


Figure 186: Need for re-intervention at ≥12 months (48 h)

Figure 187: Re-hospitalisation (hospitalisation for heart failure) at ≥12 months (12 months)

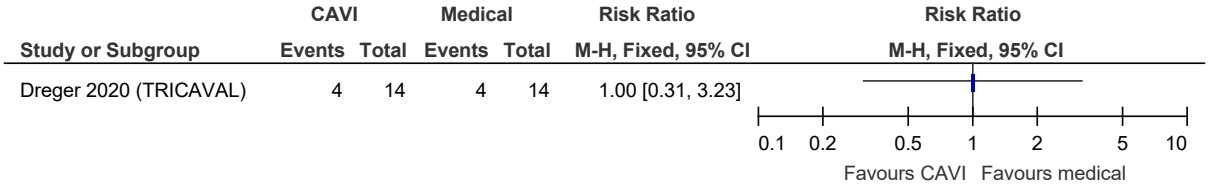
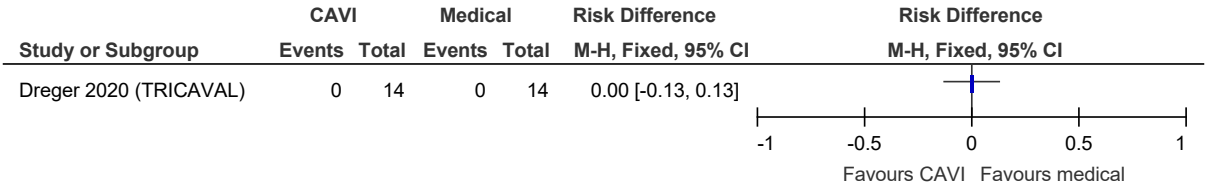


Figure 188: Intervention-related major vascular complications at 30 days



1

Appendix F: GRADE tables

F.1 Aortic stenosis (non-bicuspid)

Table 44: Clinical evidence profile: Minimally invasive surgery replacement vs. standard surgery replacement

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive surgery replacement	standard surgery replacement	Relative (95% CI)	Absolute		
All-cause mortality at ≥12 months (follow-up mean 294 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/60 (5%)	3.3%	RR 1.5 (0.26 to 8.66)	16 more per 1000 (from 24 fewer to 253 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related mortality at 30 days (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/60 (1.7%)	0%	OR 7.39 (0.15 to 372.38)	20 more per 1000 (from 30 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≥12 months												
0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at ≥12 months												

0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days (follow-up postoperative)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/60 (1.7%)	0%	OR 7.39 (0.15 to 372.38)	20 more per 1000 (from 30 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding (reoperation for bleeding) at 30 days (follow-up postoperative)												
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	5/60 (8.3%)	5%	RR 1.67 (0.42 to 6.66)	33 more per 1000 (from 29 fewer to 283 more)	⊕OOO VERY LOW	CRITICAL
Need for reintervention at ≥12 months (reoperation for paravalvular leakage) (follow-up mean 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/60 (1.7%)	0%	OR 7.39 (0.15 to 372.38)	20 more per 1000 (from 30 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation (pacing wire implantation) at 30 days (follow-up postoperative)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/60 (23.3%)	26.7%	RR 0.88 (0.47 to 1.63)	32 fewer per 1000 (from 142 fewer to 168 more)	⊕OOO VERY LOW	IMPORTANT
Intervention-related AF (supraventricular arrhythmias) at 30 days (follow-up postoperative)												
1	randomised trials	serious[1]	no serious inconsistency	serious[5]	no serious imprecision	none	1/60 (1.7%)	26.7%	RR 0.06 (0.01 to 0.46)	251 fewer per 1000 (from 144 fewer to 264 fewer)	⊕⊕OO LOW	IMPORTANT

Intervention-related major vascular complications at 30 days												
0	No evidence available											IMPORTANT
Prosthetic valve endocarditis at ≥12 months (follow-up mean 294 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/60 (5%)	0%	OR 7.65 (0.78 to 74.93)	50 more per 1000 (from 10 fewer to 110 more)[3]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated manually using risk difference as zero events in at least one arm of the study
[4] Downgraded by 1 increment as major bleeding that didn't require reoperation may not be captured in this outcome
[5] Downgraded by 1 increment as outcome defined as supraventricular arrhythmias, which could include events other than atrial fibrillation

Table 45: Clinical evidence profile: Transcatheter replacement vs. standard surgery replacement

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Transcatheter replacement**	**standard surgery replacement**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≥12 months (follow-up 2-6 years)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	162/1032 (15.7%)	14.8%	RR 1.07 (0.88 to 1.31)	10 more per 1000 (from 18 fewer to 46 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality at ≥12 months (time-to-event) (follow-up 1-5 years)												
4	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	878/2246 (39.1%)	32.6%	HR 1.03 (0.93 to 1.13)	8 more per 1000 (from 19 fewer to 34 more)	⊕⊕OO LOW	CRITICAL

Cardiac mortality at ≥12 months (follow-up 2-5 years)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	246/1386 (17.7%)	16.2%	RR 1.12 (0.96 to 1.31)	19 more per 1000 (from 6 fewer to 50 more)	⊕⊕⊕O MODERATE	CRITICAL
Cardiac mortality at ≥12 months (time-to-event) (follow-up 1-5 years)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	383/1898 (20.2%)	18.9%	HR 0.99 (0.85 to 1.15)	2 fewer per 1000 (from 26 fewer to 25 more)	⊕⊕OO LOW	CRITICAL
Intervention-related mortality at 30 days (follow-up 30 days)												
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	89/3297 (2.7%)	3.1%	RR 0.88 (0.66 to 1.16)	4 fewer per 1000 (from 11 fewer to 5 more)	⊕⊕OO LOW	CRITICAL
Quality of life (KCCQ summary) at ≥12 months - mix of change and final values (follow-up 1-5 years; range of scores: 0-100; Better indicated by higher values)												
5	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	2370	2123	-	MD 1.09 higher (0.21 lower to 2.40 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (SF-12/SF-36 mental summary) at ≥12 months - mix of change and final values (follow-up 1-5 years; range of scores: 0-100; Better indicated by higher values)												
5	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	1483	1274	-	MD 0.33 lower (1.15 lower to 0.49 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at ≥12 months (SF-12/SF-36 physical summary) - mix of change and final values (follow-up 3 months - 5 years; range of scores: 0-100; Better indicated by higher values)												
6	randomised trials	very serious[1]	serious[6]	no serious indirectness	no serious imprecision[7]	none	2232	1901	-	MD 0.49 higher (0.51 lower to 1.5 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (EQ-5D utility) at ≥12 months - mix of change and final values (follow-up 3 months - 2 years; range of scores: 0-1; Better indicated by higher values)												
5	randomised trials	very serious[1]	no serious inconsistency	serious[8]	no serious imprecision[9]	none	2397	2016	-	MD 0 higher (0.01 lower to 0.01 higher)	⊕OOO VERY LOW	CRITICAL

Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days												
7	randomised trials	serious[1]	serious[6]	no serious indirectness	very serious[2]	none	142/3297 (4.3%)	4.9%	RR 0.91 (0.60 to 1.37)	4 fewer per 1000 (from 20 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days												
7	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[2]	none	380/3276 (11.6%)	25.3%	RR 0.51 (0.27 to 0.95)	124 fewer per 1000 (from 13 fewer to 185 fewer)	⊕OOO VERY LOW	CRITICAL
Need for reintervention at ≥12 months (follow-up 30 days - 5 years)												
5	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/2460 (2.4%)	0.7%	RR 3.81 (2.17 to 6.7)	20 more per 1000 (from 8 more to 40 more)	⊕⊕OO LOW	CRITICAL
Need for reintervention at 12 months (time-to-event) - HR (follow-up 5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/1011 (2.1%)	0.59%	HR 3.28 (1.32 to 8.15)	13 more per 1000 (from 2 more to 41 more)	⊕⊕OO LOW	CRITICAL
Length of stay post-intervention (Better indicated by lower values)												
3	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[2,10]	none	1036	966	-	MD 2.41 lower (5.33 lower to 0.51 higher)	⊕OOO VERY LOW	IMPORTANT
Rehospitalisation at ≥12 months (follow-up 2-5 years)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	339/1603 (21.1%)	15.9%	RR 1.34 (1.16 to 1.55)	54 more per 1000 (from 25 more to 87 more)	⊕OOO VERY LOW	IMPORTANT

Rehospitalisation at ≥12 months (time-to-event) (follow-up 1-5 years)												
2	randomised trials	very serious[1]	serious[6]	serious[11]	very serious[2]	none	317/1507 (21%)	17.5%	HR 0.94 (0.49 to 1.82)	10 fewer per 1000 (from 85 fewer to 120 more)	⊕OOO VERY LOW	IMPORTANT
Intervention-related pacemaker implantation at 30 days												
7	randomised trials	serious[1]	serious[6]	no serious indirectness	no serious imprecision	none	478/3282 (14.6%)	5.7%	RR 2.43 (1.39 to 4.25)	82 more per 1000 (from 22 more to 185 more)	⊕⊕OO LOW	IMPORTANT
Intervention-related AF at 30 days												
6	randomised trials	serious[1]	serious[6]	no serious indirectness	no serious imprecision	none	322/3169 (10.2%)	32.9%	RR 0.31 (0.24 to 0.41)	227 fewer per 1000 (from 194 fewer to 250 fewer)	⊕⊕OO LOW	IMPORTANT
Major vascular complications at 30 days												
7	randomised trials	serious[1]	serious[6]	no serious indirectness	no serious imprecision	none	218/3288 (6.6%)	2.8%	RR 2.82 (1.77 to 4.49)	51 more per 1000 (from 22 more to 98 more)	⊕⊕OO LOW	IMPORTANT
Prosthetic valve endocarditis at ≥12 months (follow-up 1-5 years)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50/2391 (2.1%)	1.6%	RR 1.29 (0.85 to 1.96)	5 more per 1000 (from 2 fewer to 15 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment as one study included >10% of participants that had received previous aortic valve repair. Also, another study included <25% that had minimally invasive rather than standard surgical replacement.
[4] MIDs used to assess imprecision were ±10.91
[5] MIDs used to assess imprecision were ±3.00
[6] Downgraded by 1 increment as heterogeneity is present that cannot be explained by subgroup analysis.
[7] MIDs used to assess imprecision were ±2.00
[8] Downgraded by 1 increment as one study included >10% of participants that had received previous aortic valve repair. Also, another study only had 3 months follow-up for this outcome.
[9] MIDs used to assess imprecision were ±0.03

[10] MIDs used to assess imprecision were ±4.015
[11] Downgraded 1 by increment as <25% of the surgery arm received minimally invasive surgery rather than standard surgery

Table 46: Clinical evidence profile: Transcatheter replacement vs. pharmacological management

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter replacement	pharmacological management	Relative (95% CI)	Absolute		
All-cause mortality at ≥12 months (follow-up 5 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	127/179 (70.9%)	83.2%	HR 0.5 (0.39 to 0.64)	242 fewer per 1000 (from 151 fewer to 331 fewer)	⊕⊕OO LOW	CRITICAL
Cardiac mortality at ≥12 months (follow-up 5 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	84/179 (46.9%)	65.9%	HR 0.41 (0.31 to 0.54)	302 fewer per 1000 (from 218 fewer to 375 fewer)	⊕⊕OO LOW	CRITICAL
Intervention-related mortality at 30 days (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/179 (5%)	2.8%	RR 1.8 (0.62 to 5.27)	22 more per 1000 (from 11 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≥12 months												
0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at ≥12 months												

0	No evidence available											CRITICAL
Intervention-related stroke or TIA (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12/179 (6.7%)	1.7%	RR 4 (1.15 to 13.93)	51 more per 1000 (from 3 more to 220 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	30/179 (16.8%)	3.9%	RR 4.29 (1.93 to 9.5)	128 more per 1000 (from 36 more to 331 more)	⊕⊕OO LOW	CRITICAL
Need for reintervention at ≥12 months (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	5/179 (2.8%)	48.6%	RR 0.06 (0.02 to 0.14)	457 fewer per 1000 (from 418 fewer to 476 fewer)	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation at ≥12 months (follow-up 5 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	53/179 (29.6%)	53.1%	HR 0.4 (0.29 to 0.55)	270 fewer per 1000 (from 190 fewer to 334 fewer)	⊕⊕OO LOW	IMPORTANT
Intervention-related pacemaker implantation at 30 days (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	6/179 (3.4%)	5%	RR 0.67 (0.24 to 1.83)	16 fewer per 1000 (from 38 fewer to 42 more)	⊕OOO VERY LOW	IMPORTANT
Intervention-related AF at 30 days (follow-up 30 days)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/179 (0.56%)	1.1%	OR 0.51 (0.05 to 4.95)	5 fewer per 1000 (from 10 fewer to 41 more)	⊕OOO VERY LOW	IMPORTANT
Major vascular complications (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	29/179 (16.2%)	1.1%	RR 14.5 (3.51 to 59.86)	148 more per 1000 (from 28 more to 647 more)	⊕⊕OO LOW	IMPORTANT
Prosthetic valve endocarditis at ≥12 months (follow-up 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/179 (1.7%)	0.6%	RR 3 (0.32 to 28.57)	12 more per 1000 (from 4 fewer to 165 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as >10% of participants had previous surgical intervention (balloon aortic valvuloplasty)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 47: Clinical evidence profile: Transcatheter replacement vs. surgical replacement (unclear/mixed invasiveness)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Transcatheter replacement**	**surgery replacement (unclear/mixed invasiveness)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≥12 months (follow-up 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	33/734 (4.5%)	4.5%	RR 1 (0.62 to 1.6)	0 fewer per 1000 (from 17 fewer to 27 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months (follow-up 12 months)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	13/734 (1.8%)	2.6%	RR 0.68 (0.34 to 1.38)	8 fewer per 1000 (from 17 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	4/734 (0.54%)	1.4%	OR 0.42 (0.15 to 1.21)	8 fewer per 1000 (from 12 fewer to 3 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (KCCQ summary) at ≥12 months (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision[4]	none	429	349	-	MD 0.5 lower (2.27 lower to 1.27 higher)	⊕OOO VERY LOW	CRITICAL
Onset or exacerbation of heart failure at ≥12 months (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	24/734 (3.3%)	6.5%	RR 0.5 (0.31 to 0.81)	32 fewer per 1000 (from 12 fewer to 45 fewer)	⊕OOO VERY LOW	CRITICAL
Intervention-related stroke or TIA (all stroke) at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	25/734 (3.4%)	3.4%	RR 1 (0.58 to 1.72)	0 fewer per 1000 (from 14 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related stroke or TIA (TIA) at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	4/734 (0.54%)	0.5%	OR 1 (0.25 to 4.01)	0 fewer per 1000 (from 4 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	18/734 (2.5%)	7.5%	RR 0.33 (0.19 to 0.55)	50 fewer per 1000 (from 34 fewer to 61 fewer)	⊕OOO VERY LOW	CRITICAL
Need for reintervention (aortic reintervention) at ≥12 months (follow-up 12 months)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5/734 (0.68%)	0.5%	OR 1.25 (0.34 to 4.64)	1 more per 1000 (from 3 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	128/734 (17.4%)	6.1%	RR 2.84 (2.06 to 3.93)	112 more per 1000 (from 65 more to 179 more)	⊕OOO VERY LOW	IMPORTANT
Intervention-related AF at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	57/734 (7.8%)	35.4%	RR 0.22 (0.17 to 0.29)	276 fewer per 1000 (from 251 fewer to 294 fewer)	⊕OOO VERY LOW	IMPORTANT
Major vascular complications at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	28/734 (3.8%)	3.3%	RR 1.17 (0.68 to 1.99)	6 more per 1000 (from 11 fewer to 33 more)	⊕OOO VERY LOW	IMPORTANT
Prosthetic valve endocarditis at ≥12 months (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/734 (0.27%)	0.4%	OR 0.67 (0.12 to 3.87)	1 fewer per 1000 (from 4 fewer to 11 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as invasiveness of surgery in surgery group is unclear
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] MIDs used to assess imprecision were ±10.63

1

F.2 Aortic stenosis (bicuspid)

3 No evidence identified for this stratum.

F.3 Aortic stenosis (mixed non-bicuspid and bicuspid or unclear)

5 **Table 48: Clinical evidence profile: Minimally invasive surgery replacement vs. standard surgery replacement**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	minimally invasive surgery replacement	standard surgery replacement	Relative (95% CI)	Absolute		
All-cause mortality at ≥12 months (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/49 (8.2%)	6.3%	RR 1.31 (0.31 to 5.53)	20 more per 1000 (from 43 fewer to 285 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months												
2	randomised trials	serious[1]	serious[3]	no serious indirectness	very serious[2]	none	4/69 (5.8%)	5%	RR 1.59 (0.12 to 21.43)	30 more per 1000 (from 80 fewer to 130 more)[4]	⊕OOO VERY LOW	CRITICAL

Intervention-related mortality at 30 days (follow-up 7-30 days)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/176 (3.4%)	4%	RR 0.79 (0.30 to 2.08)	10 fewer per 1000 (from 50 fewer to 30 more)[4]	⊕OOO VERY LOW	CRITICAL
Quality of life (EQ-5D) at ≥12 months (follow-up 3 months; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2,5]	none	46	48	-	MD 0 higher (0.04 lower to 0.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (EQ-5D-5L index) at 12 months (follow-up 12 months; range of scores: -0.654-1.00; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	47	47	-	MD 0.02 higher (0.03 lower to 0.07 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (EQ-5D-5L utilities - health index) at 12 months (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2,7]	none	47	47	-	MD 1.60 higher (2.27 lower to 5.47 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (EQ-5D-5L utilities - severity index) at 12 months (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	47	47	-	MD 1.70 lower (5.57 lower to 2.17 higher)	⊕⊕OO LOW	CRITICAL

Quality of life (EQ-5D-5L utilities - visual scale) at 12 months (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,9]	none	47	47	-	MD 1.08 lower (7.55 lower to 5.39 higher)	⊕OOO VERY LOW	CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days (follow-up 30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/115 (3.5%)	2%	RR 1.88 (0.41 to 8.58)	20 more per 1000 (from 30 fewer to 60 more)[4]	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days (follow-up 72 h - 30 days)												
4	randomised trials	serious[1]	no serious inconsistency	serious[10]	very serious[2]	none	26/153 (3.9%)	6.6%	RR 0.85 (0.57 to 1.27)	30 fewer per 1000 (from 110 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Need for re-intervention at ≥12 months (follow-up 7-30 days)												
5	randomised trials	very serious[1]	no serious inconsistency	serious[11]	very serious[2]	none	7/173 (3.3%)	4.0%	RR 1.04 (0.40 to 2.69)	0 more per 1000 (from 40 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL

Length of hospital stay (days) (follow-up in-hospital - 30 days; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[12]	none	108	109	-	MD 0.2 lower (0.65 lower to 0.25 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Length of hospital stay (days) (follow-up 30 days; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	21	-	Median 1 day higher	⊕⊕⊕O MODERATE	IMPORTANT
Length of intensive care unit stay (days) (follow-up in-hospital; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,13]	none	50	50	-	MD 1.41 lower (3.48 lower to 0.66 higher)	⊕OOO VERY LOW	IMPORTANT
Re-hospitalisation at ≥12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days (follow-up 30 days)												
3	randomised trials	serious[1]	serious[3]	no serious indirectness	very serious[2]	none	3/115 (2.6%)	6.0%	RR 0.70 (0.11 to 4.66)	10 fewer per 1000 (from 90 fewer to 60 more)[4]	⊕OOO VERY LOW	IMPORTANT

New-onset atrial fibrillation at 30 days (follow-up 30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24/89 (28.2%)	28.6%	RR 0.99 (0.61 to 1.58)	3 fewer per 1000 (from 112 fewer to 166 more)	⊕OOO VERY LOW	IMPORTANT
Intervention-related major vascular complications at 30 days												
0	No evidence available											IMPORTANT
Prosthetic valve endocarditis at ≥12 months (follow-up 12 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[14]	none	1/93 (1.1%)	1.1%	RD 0 (-0.04 to 0.04)	0 fewer per 1000 (from 40 fewer to 40 more)[15]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment because of heterogeneity that cannot be explain by subgroup analysis
[4] Absolute effect calculated manually using risk difference as zero events in one arm of some studies
[5] MIDs used to assess imprecision were ±0.03
[6] MIDs used to assess imprecision were ±0.075
[7] MIDs used to assess imprecision were ±1.03
[8] MIDs used to assess imprecision were ±6.00
[9] MIDs used to assess imprecision were ±7.21
[10] Downgraded by 1 increment as the study with the most weighting in the meta-analysis reports transfusion only and unclear whether captures all major bleeding events
[11] Downgraded because the outcome was reported at <3 months follow-up
[12] MIDs used to assess imprecision were ±1.20
[13] MIDs used to assess imprecision were ±3.425
[14] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[15] Absolute effect calculated manually using risk difference due to zero events in both arms of one of the studies

F.4 Aortic regurgitation (non-bicuspid)

No evidence identified for this stratum.

F.5 Aortic regurgitation (bicuspid)

No evidence identified for this stratum.

F.6 Aortic regurgitation (mixed non-bicuspid and bicuspid or unclear)

No evidence identified for this stratum.

F.7 Mixed/unclear aortic valve disease

Table 49: Clinical evidence profile: Minimally invasive surgery replacement vs. standard surgery replacement

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive surgical replacement	Conventional surgical replacement	Relative (95% CI)	Absolute		
All-cause mortality (time to event) at ≥12 months (follow-up 12-30 months)												
1	randomised trials	very serious[1]	serious[2]	serious[3]	very serious[4]	none	unclear	8.14%[5]	HR 1.50 (0.61 to 3.71)[4]	38 more per 1000 (from 31 fewer to 189 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality (dichotomous) at ≥12 months (follow-up 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	3/49 (6.1%)	3/49 (6.1%)	RR 1 (0.21 to 4.71)	0 fewer per 1000 (from 48 fewer to 227 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months (follow-up postoperative - 2 years)												

3	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[6]	none	10/174 (5.7%)	3.5%	RD 0.02 (-0.02 to 0.07)	20 more per 1000 (from 20 fewer to 70 more)[7]	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality up to 30 days (follow-up <30 days/postoperative)												
5	randomised trials	very serious[1]	no serious inconsistency	serious3	very serious[6]	none	6/272 (2.8%)	1.9%	RD 0.00 (-0.02 to 0.03)	0 fewer per 1000 (from 20 fewer to 30 more)[7]	⊕OOO VERY LOW	CRITICAL
Quality of life (EQ-5D, final value) at ≥ 12 months (follow-up 1 years; measured with: EQ-5D; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4,8]	none	103	84	-	MD 0.05 higher (0.03 lower to 0.13 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36 bodily pain, final value) at ≥ 12 months (follow-up 1 years; measured with: SF-36 bodily pain subscale; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4,9]	none	99	86	-	MD 4 higher (5.11 lower to 13.11 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36 general health, final value) at ≥12 months (follow-up 1 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4,10]	none	100	86	-	MD 6 higher (1.49 lower to 13.49 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36 mental health, final value) at ≥12 months (follow-up 1 years; measured with: SF-36 mental health; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4,9]	none	100	86	-	MD 3 higher (4.04 lower to 10.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36 physical functioning, final value) at ≥12 months (follow-up 1 years; measured with: SF-36 physical functioning; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4,9]	none	100	86	-	MD 7 higher (1.8 lower to 15.8 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36 role emotional, final value) at ≥12 months (follow-up 1 years; measured with: SF-36 role emotional; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4,11]	none	98	85	-	MD 5 higher (6.8 lower to 16.8 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36 role physical, final value) at ≥12 months (follow-up 1 years; measured with: SF-36 role physical; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4,9]	none	98	85	-	MD 12 higher (1.1 lower to 25.1 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36 social functioning, final value) at ≥12 months (follow-up 1 years; measured with: SF-36 social functioning; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4,9]	none	98	85	-	MD 3 higher (5.72 lower to 11.72 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36 vitality, final value) at ≥12 months (follow-up 1 years; measured with: SF-36 vitality; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4,10]	none	100	86	-	MD 6 higher (1.49 lower to 13.49 higher)	⊕OOO VERY LOW	CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke at 30 days (follow-up postoperative)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[6]	none	0/76 (0%)	3.9%	RD 0 (-0.10 to 0.02)	0 fewer per 1000 (from 100 fewer to 20 more)[7]	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding (re-exploration for bleeding) at 30 days (follow-up <30 days/postoperative)												
4	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	4/166 (2.4%)	7.8%	RR 0.33 (0.12 to 0.95)	50 fewer per 1000 (from 100 fewer to 10 more)[12]	⊕OOO VERY LOW	CRITICAL
Need for re-intervention at 12 months (30 months) (follow-up 30 months)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	3/56 (5.4%)	5.4%[13]	HR 0.87 (0.17 to 4.45)	7 fewer per 1000 (from 44 fewer to 164 more)	⊕OOO VERY LOW	CRITICAL
Need for re-intervention at ≥12 months (follow-up 30-354 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	6/98 (6.1%)	2.4%	RR 2.51 (0.52 to 12.1)	36 more per 1000 (from 12 fewer to 266 more)	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (final value) after intervention (Better indicated by lower values)												
7	randomised trials	serious[1]	very serious[2]	serious[3]	very serious[4,14]	none	324	310	-	MD 1.67 lower (2.73 to 0.61 lower)	⊕OOO VERY LOW	IMPORTANT
Length of intensive care unit stay (final value) after intervention (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision[15]	none	56	56	-	MD 0.10 lower (0.34 lower to 0.14 higher)	⊕OOO VERY LOW	IMPORTANT
Re-hospitalisation												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency[162]	serious[3]	very serious[4]	none	1/20 (5%)	0%	OR 7.39 (0.15 to 372.38)	50 more per 1000 (from 80 fewer to 180 more)[12]	⊕OOO VERY LOW	IMPORTANT
1	randomised trials	serious[1]	no serious inconsistency[162]	serious[3]	very serious[4]	none	0/56 (0%)	1.8%	OR 0.14 (0 to 6.82)	20 fewer per 1000 (from 70 fewer to 30 more)[12]	⊕OOO VERY LOW	IMPORTANT
Intervention-related atrial fibrillation and postoperative arrhythmias												

2	randomised trials	very serious[1]	no serious inconsistency	very serious[3,16]	very serious[4]	none	10/70 (14.3%)	22.1%	RR 0.71 (0.35 to 1.47)	64 fewer per 1000 (from 144 fewer to 104 more)	⊕OOO VERY LOW	IMPORTANT
Intervention-related major vascular complications at 30 days												
0	No evidence available											IMPORTANT
Prosthetic valve endocarditis ≥12 months												
0	No evidence available											IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment because of heterogeneity that cannot be explain by subgroup analysis
[3] Downgraded due to the type of aortic valve disease being poorly defined
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[5] Control group risk taken from events in Nair 2018 study as number of events not clear in the other study
[6] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[7] Absolute effect calculated manually using risk difference as zero events in both arms of one study.
[8] MIDs used to assess imprecision were ±0.03
[9] MIDs used to assess imprecision were ±3.00
[10] MIDs used to assess imprecision were ±2.00
[11] MIDs used to assess imprecision were ±4.00
[12] Absolute effect calculated manually using risk difference as zero events in one arm of at least one study
[13] Control group risk estimated from data in KM curves
[14] MIDs used to assess imprecision were ±1.15
[15] MIDs used to assess imprecision were ±0.35
[16] For this outcome, the point estimate of one study in opposite direction to the other study. Subgroup analyses could not be performed as only two studies. Studies therefore kept separate rather than pooling.
[17] Downgraded due to inclusion of other types of postoperative arrhythmias than atrial fibrillation

F.8 Mitral stenosis

Table 50: Clinical evidence profile: Minimally invasive surgery repair vs. standard surgery repair

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Minimally invasive surgery repair**	**standard surgery repair**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≥12 months (follow-up 7 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	0%	RD 0 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months (follow-up 7 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	0%	RD 0 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	0%	RD 0 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≥12 months												
0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	0%	RD 0 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days												

0	No evidence available											CRITICAL
Need for reintervention at ≥12 months (follow-up 7 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/30 (50%)	6.7%	RR 7.5 (1.88 to 29.99)	436 more per 1000 (from 59 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation at 12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related atrial fibrillation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related major vascular complications at 30 days												
0	No evidence available											IMPORTANT
Prosthetic valve endocarditis at ≥12 months												
0	No evidence available											IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Imprecision assessed using sample size as zero events in both arms of the study. Very serious imprecision as sample size <70.
[3] Absolute effect calculated manually using risk difference as zero events in both arms of the study

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2 **Table 51: Clinical evidence profile: Transcatheter repair vs. standard surgery repair**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MS: Transcatheter repair	standard surgery repair	Relative (95% CI)	Absolute		
All-cause mortality at ≥12 months (follow-up 3-7 years)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/60 (1.7%)	0%	RD 0.02 (-0.04 to 0.07)	20 more per 1000 (from 40 fewer to 70 more)[4]	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months (follow-up 3-7 years)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/60 (1.7%)	0%	RD 0.02 (-0.04 to 0.07)	20 more per 1000 (from 40 fewer to 70 more)[4]	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days												
2	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[5]	none	0/60 (0%)	0%	RD 0 (-0.05 to 0.05)	0 fewer per 1000 (from 50 fewer to 50 more)[4]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≥12 months												
0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days												

2	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[5]	none	0/60 (0%)	0%	RD 0 (-0.05 to 0.05)	0 fewer per 1000 (from 50 fewer to 50 more)[4]	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days												
0	No evidence available											CRITICAL
Need for reintervention at ≥12 months (follow-up 7 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	3/30 (10%)	6.7%	RR 1.5 (0.27 to 8.34)	34 more per 1000 (from 49 fewer to 492 more)	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related major vascular complications at 30 days												
0	No evidence available											IMPORTANT
Intervention-related atrial fibrillation at 30 days												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[7]	none	0/30 (0%)	0%	RD 0 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)[4]	⊕OOO VERY LOW	IMPORTANT
Prosthetic valve endocarditis at ≥12 months												

0	No evidence available											IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as some patients in one of the studies <18 years old - proportion unclear
[3] Downgraded by 2 increments as imprecision very serious based on OIS calculation
[4] Absolute effect calculated manually using risk difference as zero events in both arms of one or more studies
[5] Imprecision assessed using sample size as zero events in both arms of both studies. Serious imprecision as sample size >70 and <350
[6] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[7] Imprecision assessed using sample size as zero events in both arms of the study. Very serious imprecision as sample size <70

Table 52: Clinical evidence profile: Transcatheter repair vs. minimally invasive surgery repair

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Transcatheter repair**	**minimally invasive surgery repair**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≥12 months (follow-up unclear-8 years)												
5	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/296 (0.68%)	0%	RD 0 (-0.02 to 0.02)	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months (follow-up unclear-8 years)												
5	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/296 (0.68%)	0%	RD 0 (-0.02 to 0.02)	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days												
5	randomised trials	very serious[1]	no serious inconsistency	serious[5]	very serious[3]	none	2/297 (0.67%)	0%	RD 0 (-0.02 to 0.02)	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≥12 months												

0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days												
5	randomised trials	very serious[1]	no serious inconsistency	serious[6]	very serious[3]	none	1/295 (0.34%)	0%	RD 0 (-0.01 to 0.02)	0 fewer per 1000 (from 10 fewer to 20 more)[4]	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/118 (0.85%)	0%	RD 0 (-0.02 to 0.04)	10 more per 1000 (from 20 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Need for reintervention at ≥12 months (follow-up unclear-8 years)												
4	randomised trials	very serious[1]	serious[7]	no serious indirectness	very serious[8]	none	12/196 (6.1%)	1.2%	RR 1.13 (0.21 to 6.03)	20 fewer per 1000 (from 200 fewer to 150 more)[4]	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation at 12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related atrial fibrillation at 30 days												

0	No evidence available											IMPORTANT
Prosthetic valve endocarditis at ≥12 months												
0	No evidence available											IMPORTANT
Major vascular complications at 30 days												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/120 (9.2%)	0%	OR 8.02 (2.4 to 26.8)	90 more per 1000 (from 40 more to 150 more)[4]	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as two studies include some under 18 years old - proportion unclear. One study follow-up <3 months
[3] Downgraded by 2 increments as imprecision very serious based on OIS calculation
[4] Absolute effect calculated manually using risk difference as zero events in one or both arms of one or more studies
[5] Downgraded by 1 increment as two studies include some under 18 years old - proportion unclear.
[6] Downgraded by 1 increment as two studies include some under 18 years old - proportion unclear. Also one study reports hemiplegia rather than stroke specifically.
[7] Downgraded by 1 increment as heterogeneity is present but could not be explained by subgrouping strategies
[8] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 53: Clinical evidence profile: Transcatheter repair vs. surgical repair (unclear/mixed invasiveness)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Transcatheter repair**	**surgical repair (unclear/mixed invasiveness)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≥12 months (follow-up 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/40 (0%)	0%	RD 0 (-0.05 to 0.05)	0 fewer per 1000 (from 50 fewer to 50 more)[4]	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months (follow-up 2 years)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/40 (0%)	0%	RD 0 (-0.05 to 0.05)	0 fewer per 1000 (from 50 fewer to 50 more)[4]	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/40 (0%)	0%	RD 0 (-0.05 to 0.05)	0 fewer per 1000 (from 50 fewer to 50 more)[4]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≥12 months												
0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days												
0	No evidence available											CRITICAL
Intervention-related major bleeding at 30 days (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[5]	no serious imprecision	none	0/40 (0%)	10.3%	OR 0.12 (0.02 to 0.74)	130 fewer per 1000 (from 230 fewer to 20 fewer)[4]	⊕OOO VERY LOW	CRITICAL
Need for reintervention at ≥12 months (follow-up 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/40 (0%)	0%	RD 0 (-0.05 to 0.05)	0 fewer per 1000 (from 50 fewer to 50 more)[4]	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT

Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days (follow-up postoperative)												
1	randomised trials	serious[1]	no serious inconsistency	serious[6]	very serious[7]	none	0/40 (0%)	5.2%	OR 0.13 (0.01 to 2.15)	50 fewer per 1000 (from 130 fewer to 30 more)[4]	⊕OOO VERY LOW	IMPORTANT
Intervention-related atrial fibrillation at 30 days (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[6]	no serious imprecision	none	0/40 (0%)	10.2%	OR 0.12 (0.02 to 0.62)	150 fewer per 1000 (from 270 fewer to 30 fewer)[4]	⊕OOO VERY LOW	IMPORTANT
Major vascular complications at 30 days (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[6]	very serious[7]	none	2/40 (5%)	0%	OR 7.58 (0.47 to 123.37)	50 more per 1000 (from 30 fewer to 130 more)[4]	⊕OOO VERY LOW	IMPORTANT
Prosthetic valve endocarditis at ≥12 months												
0	No evidence available											IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as some patients were <18 years old - proportion unclear
[3] Imprecision assessed using sample size as zero events in both arms of the study. Serious imprecision as sample size >70 and <350
[4] Absolute effect calculated manually using risk difference as zero events in at least one arm of one or more studies
[5] Downgraded by 1 increment as some patients in the study were <18 years old - proportion unclear. Also time-point measured at for this outcome unclear and unclear whether all were major bleeding events
[6] Downgraded by 1 increment as some patients in the study were <18 years old - proportion unclear. Also time-point measured at for this outcome unclear.
[7] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

F.9 Mitral regurgitation

2 **Table 54: Clinical evidence profile: Standard surgery replacement vs. standard surgery repair**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MR: Standard surgery replacement	standard surgery repair	Relative (95% CI)	Absolute		
All-cause mortality at ≥12 months												
0	No evidence available											CRITICAL
Cardiac mortality at ≥12 months (follow-up in-hospital)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/40 (2.5%)	5%	RR 0.5 (0.05 to 5.3)	25 fewer per 1000 (from 47 fewer to 215 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days (follow-up in-hospital)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/40 (2.5%)	5%	RR 0.5 (0.05 to 5.3)	25 fewer per 1000 (from 47 fewer to 215 more)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≥12 months												
0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days (follow-up in-hospital)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[3]	none	1/40 (2.5%)	2.5%	RR 1 (0.06 to 15.44)	0 fewer per 1000 (from 24 fewer to 361 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days												
0	No evidence available											CRITICAL
Need for reintervention at ≥12 months (follow-up in-hospital)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/40 (2.5%)	7.5%	RR 0.33 (0.04 to 3.07)	50 fewer per 1000 (from 72 fewer to 155 more)	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related atrial fibrillation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related major vascular complications at 30 days												
0	No evidence available											IMPORTANT
Prosthetic valve endocarditis at ≥12 months												

0	No evidence available											IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded for indirectness as follow-up was <3 months
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded for indirectness as neurological dysfunction could include events other than stroke and TIA

Table 55: Clinical evidence profile: Minimally invasive surgery repair vs. standard surgery repair

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Minimally invasive surgery repair**	**standard surgery repair**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≥12 months (follow-up 3 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/79 (3.8%)	3.8%	RR 1.01 (0.21 to 4.87)	0 more per 1000 (from 30 fewer to 147 more)	⊕⊕OO LOW	CRITICAL
Cardiac mortality at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related mortality at 30 days (follow-up intraoperative/early postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/80 (2.5%)	2.5%	RR 1 (0.14 to 6.93)	0 fewer per 1000 (from 22 fewer to 148 more)	⊕⊕OO LOW	CRITICAL
Quality of life at ≥12 months (SF-36 general health domain) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1,3]	none	76	77	-	MD 1.3 lower (4.22 lower to 1.62 higher)	⊕⊕OO LOW	CRITICAL

Quality of life at ≥12 months (SF-36 mental health domain) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1,4]	none	76	77	-	MD 0.9 higher (1.99 lower to 3.79 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at ≥12 months (SF-36 physical activity domain) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1,4]	none	76	77	-	MD 0.6 lower (3.41 lower to 2.21 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at ≥12 months (SF-36 role limitation domain) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1,4]	none	76	77	-	MD 1 lower (4.05 lower to 2.05 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at ≥12 months (SF-36 social activities domain) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	76	77	-	MD 0.4 higher (1.82 lower to 2.62 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at ≥12 months (SF-36 vitality domain) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1,3]	none	76	77	-	MD 1 higher (1.66 lower to 3.66 higher)	⊕⊕OO LOW	CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days (follow-up intraoperative/early postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[5]	very serious[1]	none	1/70 (1.4%)	2.9%	RR 0.5 (0.05 to 5.39)	15 fewer per 1000 (from 28 fewer to 127 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days (follow-up intraoperative/early postoperative)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/70 (5.7%)	4.3%	RR 1.33 (0.31 to 5.74)	14 more per 1000 (from 30 fewer to 204 more)	⊕⊕OO LOW	CRITICAL
Need for reintervention at ≥12 months (follow-up 3 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/76 (2.6%)	1.3%	RR 2.03 (0.19 to 21.88)	13 more per 1000 (from 11 fewer to 271 more)	⊕⊕OO LOW	CRITICAL
Length of hospital stay post-intervention (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,6]	none	80	80	-	MD 3.1 lower (4.57 to 1.63 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related atrial fibrillation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related major vascular complications at 30 days												
0	No evidence available											IMPORTANT
Prosthetic valve endocarditis at ≥12 months (follow-up 3 years)												
1	randomised trials	serious[2]	no serious inconsistency	serious[7]	serious[8]	none	0/76 (0%)	0%	RD 0 (-0.03 to 0.03)[9]	0 fewer per 1000 (from 30 fewer to 30 more)[10]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] MIDs used to assess imprecision were ±2.00
[4] MIDs used to assess imprecision were ±3.00
[5] Downgraded as neurological complications may include events other than stroke and TIA
[6] MIDs used to assess imprecision were ±2.50
[7] Downgraded as outcome may not be prosthetic valve endocarditis as specified in the protocol based on the interventions being repair rather than replacement procedures
[8] Imprecision assessed using sample size as zero events in both arms - serious imprecision as sample size is >70 and <350
[9] Presented as risk difference
[10] Absolute effect calculated manually using risk difference as zero events in both arms.

Table 56: Clinical evidence profile: Minimally invasive surgery (mixed repair/replacement) vs. standard surgery (mixed repair/replacement)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**minimally invasive surgery (mixture of repair and replacement)**	**standard surgery (mixture of repair and replacement)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≥12 months												
0	No evidence available											CRITICAL
Cardiac mortality at ≥12 months (follow-up in-hospital)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	0/20 (0%)	0%	RD 0 (-0.09 to 0.09)[4]	0 fewer per 1000 (from 90 fewer to 90 more)[5]	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days (follow-up in-hospital)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[6]	very serious[3]	none	0/20 (0%)	0%	RD 0 (-0.09 to 0.09)[4]	0 fewer per 1000 (from 90 fewer to 90 more)[5]	⊕OOO VERY LOW	CRITICAL

Health-related quality of life at ≥12 months												
0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at ≥12 months (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[2]	very serious[7]	none	1/20 (5%)	5%	RR 1 (0.07 to 14.9)	0 fewer per 1000 (from 47 fewer to 695 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related stroke or TIA at 30 days (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/20 (5%)	5%	RR 1 (0.07 to 14.9)	0 fewer per 1000 (from 47 fewer to 695 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[6]	very serious[3]	none	0/20 (0%)	5%	OR 0.14 (0 to 6.82)	50 fewer per 1000 (from 180 fewer to 80 more)[8]	⊕OOO VERY LOW	CRITICAL
Need for reintervention at ≥12 months												
0	No evidence available											CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days (follow-up postoperative)												

1	randomised trials	very serious[1]	no serious inconsistency	very serious[6]	very serious[7]	none	0/20 (0%)	5%	OR 0.14 (0 to 6.82)	50 fewer per 1000 (from 180 fewer to 80 more)[8]	⊕OOO VERY LOW	IMPORTANT
Intervention-related atrial fibrillation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related major vascular complications at 30 days												
0	No evidence available											IMPORTANT
Prosthetic valve endocarditis at ≥12 months												
0	No evidence available											IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded 2 increments as indirect population and interventions: proportion with mitral stenosis rather than mitral regurgitation and mixture of repair and replacement interventions within each study arm. In addition, follow-up <3 months.
[3] Imprecision assessed using sample size as zero events in both arms of the study. Very serious imprecision as sample size <70.
[4] Presented as risk difference
[5] Absolute effect calculated manually using risk difference as zero events in both arms of the study
[6] Downgraded 2 increments as indirect population and interventions: proportion with mitral stenosis rather than mitral regurgitation and mixture of repair and replacement interventions within each study arm.
[7] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[8] Absolute effect calculated manually using risk difference as zero events in one arm of the study

Table 57: Clinical evidence profile: Surgical replacement (unclear/mixed invasiveness) vs. surgical repair (unclear/mixed invasiveness)

Quality assessment					No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical replacement (unclear/mixed invasiveness)	surgical repair (unclear/mixed invasiveness)	Relative (95% CI)	Absolute		
All-cause mortality at ≥12 months (time to event, 24 months) - HR (follow-up 2 years)												
2	randomised trials	serious[1]	serious[2]	serious[3]	very serious[4]	none	-	11.75%	HR 1.95 (0.64 to 5.94)	99 more per 1000 (from 41 fewer to 407 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months (follow-up 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4]	none	8/47 (17%)	2.4%	RR 6.98 (0.91 to 53.47)	144 more per 1000 (from 2 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days												
2	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	6/172 (3.5%)	0.8%	RR 2.54 (0.6 to 10.77)	20 more per 1000 (from 1 fewer to 60 more)[5]	⊕OOO VERY LOW	CRITICAL
Quality of life at ≥12 months (EQ-5D) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision[6]	none	80	91	-	MD 0.2 higher (5.33 lower to 5.73 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at ≥12 months (MLWHF questionnaire) (follow-up 12 months; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4,7]	none	85	95	-	MD 4.9 lower (11.11 lower to 1.31 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at ≥12 months (SF-12 mental function) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision[8]	none	85	93	-	MD 0.1 higher (1.88 lower to 2.08 higher)	⊕OOO VERY LOW	CRITICAL

Quality of life at ≥12 months (SF-12 physical function) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision[9]	none	85	93	-	MD 0.6 higher (1.63 lower to 2.83 higher)	⊕OOO VERY LOW	CRITICAL
Onset or exacerbation of heart failure at ≥12 months (follow-up 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	5/84 (6%)	5.9%	RR 1.01 (0.3 to 3.37)	1 more per 1000 (from 41 fewer to 140 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related stroke or TIA at 30 days												
2	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	5/172 (2.9%)	1.2%	RR 1.54 (0.41 to 5.81)	10 more per 1000 (from 20 fewer to 50 more)[5]	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	1/47 (2.1%)	0%	OR 6.5 (0.13 to 330.77)	20 more per 1000 (from 40 fewer to 80 more)[5]	⊕OOO VERY LOW	CRITICAL
Need for reintervention at ≥12 months (24 months) (follow-up 2 years)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	1/169 (0.59%)	7.4%	OR 0.17 (0.06 to 0.49)	70 fewer per 1000 (from 30 fewer to 110 fewer)[5]	⊕OOO VERY LOW	CRITICAL
Length of stay post-intervention (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision[10]	none	125	126	-	MD 0.4 higher (1.78 lower to 2.58 higher)	⊕⊕OO LOW	IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT

Intervention-related pacemaker implantation at 30 days (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	3/47 (6.4%)	4.9%	RR 1.31 (0.23 to 7.45)	15 more per 1000 (from 38 fewer to 316 more)	⊕OOO VERY LOW	IMPORTANT
Major vascular complications at 30 days (follow-up intraoperative)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	1/47 (2.1%)	2.4%	RR 0.87 (0.06 to 13.51)	3 fewer per 1000 (from 23 fewer to 300 more)	⊕OOO VERY LOW	IMPORTANT
Prosthetic valve endocarditis at ≥12 months (follow-up 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	2/125 (1.6%)	0%	OR 7.51 (0.47 to 120.72)	20 more per 1000 (from 10 fewer to 40 more)[5]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment because heterogeneity is present and subgrouping strategies cannot be used due to there being only two studies in the meta-analysis: I2=62%, p=0.10.
[3] Downgraded by 1 increment as the interventions are indirect due to there being a mixture of minimally invasive and standard surgery replacement
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[5] Absolute effect calculated manually using risk difference as zero events in one arm of one of the studies
[6] MIDs used to assess imprecision were ±11.98
[7] MIDs used to assess imprecision were ±5.0
[8] MIDs used to assess imprecision were ±4.2
[9] MIDs used to assess imprecision were ±3.83
[10] MIDs used to assess imprecision were ±4.50

Table 58: Clinical evidence profile: Transcatheter repair vs. pharmacological management

Quality assessment						No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter repair	pharmacological management	Relative (95% CI)	Absolute		
All-cause mortality at ≥12 months (time-to-event) - HR (follow-up 24 months)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	133/454	37.3%	HR 0.78 (0.48 to 1.28)	68 fewer per 1000 (from 172 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality at ≥12 months (dichotomous) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/81 (13.6%)	17.2%	RR 0.79 (0.3 to 2.07)	36 fewer per 1000 (from 120 fewer to 184 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months (time-to-event) - HR (follow-up 24 months)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	108/454 (23.8%)	31.3%	HR 0.75 (0.45 to 1.25)	68 fewer per 1000 (from 158 fewer to 62 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	7/239 (2.9%)	2.2%	RR 1.35 (0.41 to 4.45)	10 more per 1000 (from 20 fewer to 40 more)[4]	⊕⊕OO LOW	CRITICAL
Quality of life at ≥12 months (EQ-5D) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	93	87	-	MD 2.2 higher (3.43 lower to 7.83 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at ≥12 months (KCCQ overall) (follow-up 24 months; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3,6]	none	198	114	-	MD 7.13 higher (1.79 to 12.46 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at ≥12 months (SF-36 mental component) (follow-up 24 months; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3,7]	none	127	90	-	MD 1.2 higher (2.06 lower to 4.46 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at ≥12 months (SF-36 physical component) (follow-up 24 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3,8]	none	127	90	-	MD 4 higher (1.25 to 6.75 higher)	⊕OOO VERY LOW	CRITICAL
Onset of exacerbation of heart failure at ≥12 months (follow-up 12-24 months)												
3	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	201/541 (37.2%)	51.5%	RR 0.77 (0.57 to 1.03)	118 fewer per 1000 (from 221 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related stroke or TIA at 30 days (follow-up periprocedural-30 days)												
2	randomised trials	serious[1]	no serious inconsistency	serious[9]	serious[3]	none	4/446 (0.9%)	0%	OR 7.76 (1.09 to 55.28)	10 more per 1000 (from 0 more to 20 more)[10]	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days (follow-up periprocedural)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	11/152 (7.2%)	3.9%	RR 1.83 (0.7 to 4.83)	32 more per 1000 (from 12 fewer to 149 more)	⊕⊕OO LOW	CRITICAL
Need for reintervention at ≥12 months (time-to-event) - HR (follow-up 24 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/302 (3.3%)	4.8%	HR 0.61 (0.27 to 1.38)	18 fewer per 1000 (from 35 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT

Rehospitalisation at ≥12 months (time-to-event) - HR (follow-up 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	194/302 (64.2%)	73.1%	HR 0.77 (0.64 to 0.93)	95 fewer per 1000 (from 26 fewer to 163 fewer)	⊕⊕OO LOW	CRITICAL
Rehospitalisation (for HF) at 12 months (dichotomous) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	24/87 (27.6%)	36.4%	RR 0.76 (0.43 to 1.34)	87 fewer per 1000 (from 207 fewer to 124 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related pacemaker implantation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related atrial fibrillation at 30 days												
0	No evidence available											IMPORTANT
Major vascular complications at 30 days (follow-up periprocedural)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/144 (3.5%)	0%	OR 8.04 (1.37 to 46.97)	30 more per 1000 (from 0 more to 70 more)[4]	⊕⊕⊕O MODERATE	IMPORTANT
Prosthetic valve endocarditis (endocarditis) at ≥12 months (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/87 (2.3%)	0%	OR 4.02 (0.18 to 90.74)	20 more per 1000 (from 30 fewer to 80 more)[4]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment because heterogeneity is present and subgrouping strategies cannot be used due to the number of studies.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Absolute effect calculated manually using risk difference as zero events in one arm of one study
[5] MIDs used to assess imprecision were ±8.95
[6] MIDs used to assess imprecision were ±11.53

[7] MIDs used to assess imprecision were ±3.0
[8] MIDs used to assess imprecision were ±2.0
[9] Downgraded by 1 increment as gas embolism included in events for one study
[10] Absolute effect calculated manually using risk difference as zero events in one arm of both studies

Table 59: Clinical evidence profile: Transcatheter repair vs. surgery (mixed repair/replacement and unclear/mixed invasiveness)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcatheter repair	surgery (mixed repair/replacement and mixed/unclear invasiveness)	Relative (95% CI)	Absolute		
All-cause mortality at ≥12 months (follow-up 5 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	32/154 (20.8%)	26.8%	RR 0.78 (0.46 to 1.32)	59 fewer per 1000 (from 145 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related mortality at 30 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	2/180 (1.1%)	2.1%	RR 0.52 (0.07 to 3.65)	10 fewer per 1000 (from 20 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Quality of life at ≥12 months (SF-36 mental component) (follow-up 12 months; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3,4]	none	133	60	-	MD 1.9 higher (1.2 lower to 5 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at ≥12 months (SF-36 physical component) (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3,5]	none	132	60	-	MD 0 higher (3.12 lower to 3.12 higher)	⊕OOO VERY LOW	CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	2/180 (1.1%)	2.1%	RR 0.52 (0.07 to 3.65)	10 fewer per 1000 (from 20 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days												
0	No evidence available											CRITICAL
Need for reintervention at ≥12 months (follow-up 5 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	43/154 (27.9%)	8.9%	RR 3.13 (1.3 to 7.5)	190 more per 1000 (from 27 more to 578 more)	⊕⊕OO LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT

Intervention-related pacemaker implantation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related atrial fibrillation at 30 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	2/180 (1.1%)	0%	OR 4.61 (0.25 to 85.84)	10 more per 1000 (from 10 fewer to 30 more)[6]	⊕OOO VERY LOW	IMPORTANT
Major vascular complications at 30 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	very serious[3]	none	4/180 (2.2%)	4.3%	RR 0.52 (0.13 to 2.04)	21 fewer per 1000 (from 37 fewer to 45 more)	⊕OOO VERY LOW	IMPORTANT
Prosthetic valve endocarditis at ≥12 months												
0	No evidence available											IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded 1 increment as the surgical arm was a mixture of repair/replacement procedures and unclear/mixed invasiveness of surgery
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] MIDs used to assess imprecision were ±3.0
[5] MIDs used to assess imprecision were ±2.0
[6] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[7] Downgraded 2 increments as the surgical arm was a mixture of repair/replacement procedures and unclear/mixed invasiveness of surgery, and it was unclear whether events were all a result of vascular complications

F.10 Unclear/mixed mitral valve disease

Table 60: Clinical evidence profile: Minimally invasive surgery replacement vs. standard surgery replacement

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed/unclear mitral disease: minimally invasive surgery replacement**	**standard surgery replacement**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≥12 months												
0	No evidence available											CRITICAL
Cardiac mortality at ≥12 months (follow-up in-hospital/postoperative)												
2	randomised trials	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	0/67 (0%)	0%	RD 0 (-0.04 to 0.04)	0 fewer per 1000 (from 40 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days (follow-up in-hospital/postoperative)												
3	randomised trials	very serious[1]	no serious inconsistency	serious[5]	no serious imprecision	none	4/144 (2.8%)	0%	RD -0.01 (-0.05 to 0.03)	10 fewer per 1000 (from 50 fewer to 30 more)[4]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≥12 months												
0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at ≥12 months												
0	No evidence available											CRITICAL
Intervention-related stroke or TIA at 30 days (follow-up postoperative)												
1	randomised trials	serious[1]	no serious inconsistency	serious[5]	very serious[6]	none	1/77 (1.3%)	0.5%	OR 3.13 (0.14 to 70.31)	10 more per 1000 (from 4 fewer to 256 more)	⊕OOO VERY LOW	CRITICAL

Intervention-related major bleeding at 30 days												
0	No evidence available											CRITICAL
Need for reintervention at ≥12 months (follow-up postoperative)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[7]	serious[6]	none	0/77 (0%)	4.9%	OR 0.24 (0.06 to 0.99)	50 fewer per 1000 (from 80 fewer to 10 fewer)[4]	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (Better indicated by lower values)												
3	randomised trials	very serious[1]	very serious[8]	serious[5]	very serious[6,9]	none	144	271	-	MD 1.44 lower (4.09 lower to 1.22 higher)	⊕OOO VERY LOW	IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT
Intervention-related pacemaker implantation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related atrial fibrillation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related major vascular complications at 30 days												
0	No evidence available											IMPORTANT
Prosthetic valve endocarditis at ≥12 months (follow-up 2 years)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[5]	very serious[6]	none	1/69 (1.4%)	1.1%	RR 1.38 (0.13 to 14.94)	4 more per 1000 (from 10 fewer to 153 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 2 increments as the population of all studies was indirect due to it being a mixed/unclear mitral valve disease population. Also likely to be <3 months follow-up
[3] Imprecision assessed using sample size as zero events in both arms of all studies. Serious imprecision as sample size >70 and <350
[4] Absolute effect calculated manually using risk difference as zero events in at least one arm of one or more studies
[5] Downgraded by 1 increment as the population of all studies was indirect due to it being a mixed/unclear mitral valve disease population.
[6] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[7] Downgraded by 2 increments as the population of all studies was indirect due to it being a mixed/unclear mitral valve disease population. Also likely to be <3 months follow-up and the outcome is not well defined - may not be specifically valve reintervention.
[8] Downgraded by 1 increment as inconsistency is present which cannot be explain by subgrouping due to there only being three studies in the meta-analysis.
[9] MIDs used to assess imprecision were ±0.95

F.11 Tricuspid regurgitation

Table 61: Clinical evidence profile: Transcatheter repair + medical vs. medical alone

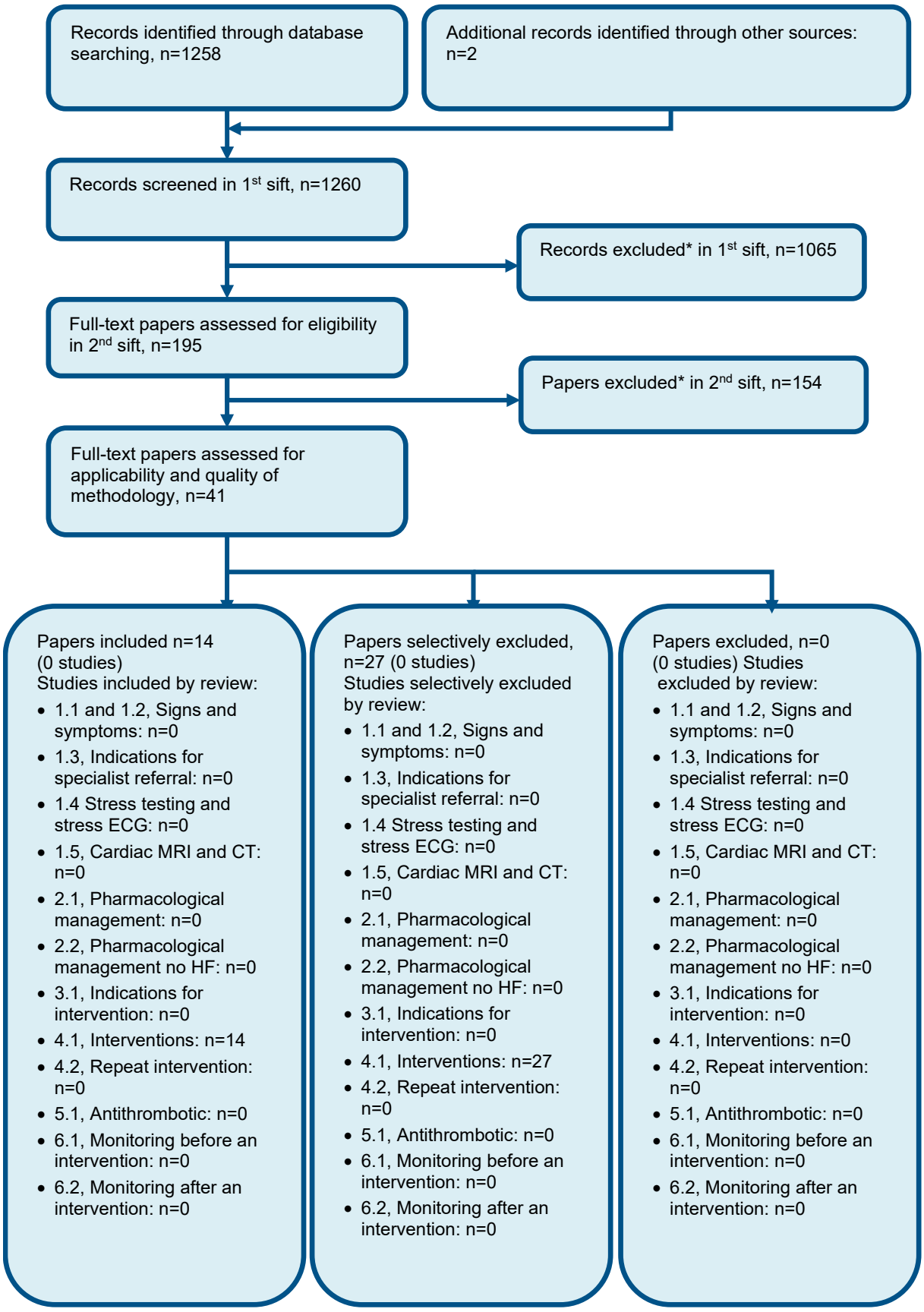
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**transcatheter repair**	**pharmacological management**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at 12 months (dichotomous) (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/14 (57.1%)	28.6%	RR 2 (0.78 to 5.14)	286 more per 1000 (from 63 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality (right heart failure) at 12 months (dichotomous) (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/14 (28.6%)	21.4%	RR 1.33 (0.36 to 4.9)	71 more per 1000 (from 137 fewer to 835 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days (in-hospital, dichotomous) (follow-up in-hospital)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/14 (21.4%)	0%	OR 8.67 (0.83 to 91.1)	214 more per 1000 (from 18 fewer to 447 more)[3]	⊕OOO VERY LOW	CRITICAL
Quality of life (MLWHF Q) at 12 months (continuous) (follow-up 3 months; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,4]	none	8	11	-	MD 12.3 lower (25.54 lower to 0.94 higher)	⊕OOO VERY LOW	CRITICAL
Onset or exacerbation of heart failure (NYHA class worsening by 1 or 2 classes) at 12 months (dichotomous) (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/8 (0%)	9.1%	OR 0.18 (0 to 9.42)	91 fewer per 1000 (from 331 fewer to 149 more)[3]	⊕OOO VERY LOW	CRITICAL
Intervention-related stroke or TIA at 30 days												
0	No evidence available											CRITICAL
Intervention-related major bleeding (haemorrhage) at 30 days (dichotomous)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/14 (7.1%)	0%	OR 7.39 (0.15 to 372.38)	71 more per 1000 (from 106 fewer to 248 more)[3]	⊕OOO VERY LOW	CRITICAL
Need for reintervention at 12 months (48 h, dichotomous) (follow-up 48 hours)												
1	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[2]	none	4/14 (28.6%)	0%	OR 9.49 (1.19 to 75.86)	286 more per 1000 (from 37 more to 535 more)[3]	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial intervention)												
0	No evidence available											IMPORTANT
Rehospitalisation (hospitalisation for HF) at 12 months (dichotomous) (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/14 (28.6%)	28.6%	RR 1 (0.31 to 3.23)	0 fewer per 1000 (from 197 fewer to 638 more)	⊕OOO VERY LOW	IMPORTANT

Intervention-related pacemaker implantation at 30 days												
0	No evidence available											IMPORTANT
Intervention-related AF at 30 days												
0	No evidence available											IMPORTANT
Major vascular complications at 30 days (dichotomous)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	0/14 (0%)	0%	RD 0 (-0.13 to 0.13)	0 fewer per 1000 (from 130 fewer to 130 more)[3]	⊕OOO VERY LOW	IMPORTANT
Prosthetic valve endocarditis at ≥12 months												
0	No evidence available											IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated manually using risk difference as 0 events in one or both arms of one study
[4] MIDs used to assess imprecision were ±5.0
[5] All events said to have occurred within 48 h and unclear if any further reinterventions occurred during follow-up
[6] Graded very serious imprecision as 0 events in both arms and sample size <70

Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

H.1 Aortic valve (non-bicuspid)

Inoperable

Study	Orlando 2013[282]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (decision tree) **Approach to analysis:** Decision tree comparing when TAVI option is available and unavailable for those suitable and unsuitable for surgery [(a)]. Following treatment, hospital-free survival and survival with 1 or more hospitalisation episodes were modelled **Perspective:** UK NHS **Time horizon:** 25-years **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** People with severe AS who cannot undergo surgery [(b)]. Cannot undergo surgery defined as those with coexisting conditions associated with a predicted probability of ≥50% of death after surgery or a serious irreversible condition. **Cohort settings for intervention 1 and 2:** Start age: 83.2 and 83.1 Male: 46.9% and 45.8% **Intervention 1:** Medical management (MM) **Intervention 2:** TAVI	**Total costs (mean per patient):** Intervention 1: £3,687 Intervention 2: £27,833 Incremental (2−1): £24,147 (95% CI: NR) **Currency & cost year:** 2010 GBP (£) **Cost components incorporated:** Short term costs include stroke, MI, arrhythmia, cardiac tamponade, bleeding, heart failure or shock, valve embolism, respiratory failure, renal dialysis, vascular complication. Other costs include initial hospital stay and procedure cost (further detail of 'procedure' not given)	**QALYs (mean per patient):** Intervention 1: 0.98 Intervention 2: 2.85 Incremental (2−1): 1.87 (95% CI: NR)	**ICER (TAVI versus MM):** £12,900 per QALY gained (95% CI: NR) **Analysis of uncertainty:** Probabilistic sensitivity analysis presented in the form of a cost-effectiveness acceptability curve. The exact number is not reported but it appears the results has >95% probability of being cost effective at a willingness to pay threshold of £20,000 per QALY gained. A number of deterministic sensitivity analyses were conducted that changed: the proportion of patients receiving an intervention due to choice or due to ineligibility, the unit costs for TAVI, short and long term mortality and quality of life scores. TAVI remained cost effective in all analyses but the ICER approached £30,000 per QALY gained when a low quality of life score was used for hospitalisation free survival

Data sources
Health outcomes: A single RCT (PARTNER-B) trial was used to inform treatment effect (the only eligible RCT for this stratum included in the clinical review). Incidence of adverse events within 30 days was taken from a literature search that largely consisted of observational data. **Quality-of-life weights**: EQ-5D or SF-36 of a Dutch mechanical aortic valve replacement population **Cost sources:** NHS Reference costs 2009-2010 were used to cost adverse events. ICU cost was calculated from the NHS reference cost list 2006-7 and inflated to 2009-10. NHS South Central Cardiovascular Network 2010 was used for the procedural cost of TAVI.
Comments
Source of funding: NIHR HTA **Limitations:** Utility data source refers to a paper that assesses both SF-36 and EQ-5D, it is not specified if EQ-5D or SF-36 has been extracted from the paper. Furthermore this paper specifically assesses utility of a Dutch population with mechanical aortic valve replacement. Observational data is used to assess the incidence of adverse events within 30 days. The PARTNER-B trial only used the Edwards SAPIEN heart-valve system; therefore generalisability of the results to other valves may be limited.
Overall applicability:[c] Directly applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: BNF = British National Formulary; CI = confidence interval; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HRQoL: health related quality of life; HTA: Health Technology Assessment; ICER= incremental cost-effectiveness ratio; ICU = intensive care unit; NIHR: National Institute for Healthcare Research; NR= not reported; NYHA = New York Heart Association; QALYs = quality-adjusted life years; RCT= randomised controlled trial; TAVI; transcatheter aortic valve replacement

(a) RCT data is only used for those unsuitable for surgery (i.e. TAVI and MM). Operable patients are also included in this study (i.e.TAVI vs surgery), however the surgery arm only uses observational data and has therefore been excluded

(b) The study defines these patients as 'unsuitable' for surgery, however, the same definition used here is considered inoperable in the PARTNER-B trial, the population is described as those who cannot undergo surgery, i.e. they are inoperable.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Watt 2012[422]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (Markov model) **Approach to analysis:** Short term Markov model with health states reflecting the location of care. Longer term Markov model health states were home care, re-operation and death. **Perspective:** UK NHS **Time horizon:** 10- year **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** People with severe AS who are cannot undergo surgery. 'Cannot undergo surgery' defined as those with coexisting conditions associated with a predicted probability of ≥50% of death after surgery or a serious irreversible condition **Cohort settings for intervention 1 and 2:** Start age: 83.2 and 83.1 Male: 46.9% and 45.8% **Intervention 1:** Medical management (MM) **Intervention 2:** Transcatheter aortic valve implantation (TAVI)	**Total costs (mean per patient):** Intervention 1: £5,000 Intervention 2: £30,200 Incremental (2−1): Intervention 2 costs £25,200 more per person (95% CI: NR) **Currency & cost year:** 2010 GBP (£) **Cost components incorporated:** TAVI and AVR devices (AVR included where conversion was necessary) and procedures, length of stay, hospitalisations pertaining to NYHA classes, medication costs	**QALYs (mean per patient):** Intervention 1: 0.80 Intervention 2: 2.36 Incremental (2−1): Intervention 2 gives 1.56 more QALYs per person (95% CI: NR)	**ICER (TAVI versus MM):** £16,100 per QALY gained (95% CI: NR) **Analysis of uncertainty:** A probabilistic sensitivity analysis suggested that TAVI had a 100% probability of being cost effective at a threshold of £20,000 per QALY gained. A series of deterministic sensitivity analyses that altered individual parameters by +/-10% found that the model was sensitive to short-term treatment effect and the cost of initial hospitalisation. Results were robust to changes in hospitalisation costs and adverse event rates.
Data sources				
Health outcomes A single RCT (PARTNER-B) trial was used to inform treatment effect (the only eligible RCT for this stratum included in the clinical review), however, where parameters were not available from PARTNER B data from a literature review including observational data was used **Quality-of-life weights**: EQ-5D UK tariff **Cost sources:** Drug costs were taken from the BNF. Procedure costs were obtained from a literature review. Other costs taken from the PSSRU or NHS Reference Costs.				
Comments				
Source of funding: funding provided by Medtronic. **Limitations:** Some parameters were informed by non-randomised data. The PARTNER-B trial only used the Edwards SAPIEN heart-valve system; therefore generalisability of the results to other valves may be limited. Appear to use the costs of the Medtronic CoreValve system, although the clinical data pertains to the Edwards SAPIEN valve system.				

Overall applicability:[(a)] Directly applicable **Overall quality:**[(b)] Potentially serious limitations

Abbreviations: AS: aortic stenosis; CI: confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost effectiveness ratio; MM: medical management; NR= not reported; NYHA: New York Heart Association; PSSRU: Personal Social Services Research Unit; QALYs= quality-adjusted life years; RCT: randomised controlled trial; TAVI: transcatheter aortic valve implantation
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitation

Inoperable/High operative Risk

Study	**Doble 2013[99]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (decision tree and Markov model) **Approach to analysis:** Decision tree for a 30-day postoperative phase and a Markov model for a long-term phase. Long term health states were Alive without complications, stroke, myocardial infarction, kidney injury and death. Model run for both inoperable and high operative risk cohorts. **Perspective:** Canadian healthcare **Time horizon:** 20-years **Discounting:** Costs: 5%; Outcomes: NR	**Population:** People with severe AS who are cannot undergo surgery[(a)] and People with severe AS who have a high risk of surgical complications[(b)] **Inoperable cohort settings:** Start age: 83 Male: NR **High risk cohort settings:** Start age: 84 Male: NR **Inoperable:** **Intervention 1** Standard therapy (including pharmacological management and balloon aortic valvuloplasty) **Intervention 2:** TF transcatheter aortic valve implantation (TAVI)	**Inoperable total costs (mean per patient):** Intervention 1: £33,323 Intervention 2: £51,161 Incremental (2−1): Intervention 2 costs £17,838 more per person (95% CI: NR) **High risk total costs (mean per patient):** Intervention 1: £42,889 Intervention 2: £49,301 Incremental (2−1): Intervention 2 costs £6,412 more per person (95% CI: NR) **Currency & cost year:** 2010 Canadian dollars presented here as 2010 GBP (£) **Cost components incorporated:** Procedural cost of index hospitalization, cost of complications, prescription costs and costs associated with long-term health states (stroke, myocardial infarction and kidney injury), costs	**Inoperable QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): Intervention 2 gives 0.85 more QALYs (95% CI: NR) **High risk QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): Intervention 2 gives 0.102 less QALYs (95% CI: NR)	**Inoperable cohort:** TF-TAVI costs £29,506 per QALY gained compared to standard therapy **High risk cohort:** TAVI is dominated by SAVR **Analysis of uncertainty:** Deterministic analyses for the inoperable cohort showed that the model was most sensitive to the procedural costs and 1-year mortality rates for both treatments. The rates of paravalvular leaks and 30-day mortality for the TF-TAVI treatment were also sensitive to change. TAVI remained dominated by SAVR in all deterministic analyses in the high risk cohort.

	High risk: **Intervention 1** Surgical aortic valve replacement (SAVR) **Intervention 2:** TF or TA Transcatheter aortic valve implantation (TAVI)	of rehospitalisation and long-term care facility stays.		Probabilistic sensitivity analyses showed that intervention 2 had a 0.441 and 0.116 probability of being cost effective at a threshold of £28,170 per QALY gained in the inoperable and high operative risk, respectively.
Data sources				
Health outcomes: A single RCT (PARTNER-B) trial was used to inform treatment effect for TAVI vs standard therapy cohort (the only eligible RCT for this comparison included in the clinical review). A single RCT (PARTNER-A) trial was used to inform the treatment effect for the TAVI vs SAVR cohort (1/7 eligible RCTs included in the clinical review). **Quality-of-life weights**: EQ-5D **Cost sources:** TAVI device costs were obtained from Edwards Lifesciences. Drug costs obtained from Ontario Drug Benefit Formulary/Comparative Drug Index 2010. Other costs derived from the Ontario Case Costing Initiative.				
Comments				
Source of funding: Monash university Grant and Health Technology Assessment Grant from the Ontario Ministry of Health and Long Term Care **Limitations:** A single RCT (PARTNER-A) trial was used to inform treatment effect for TAVI versus SAVR (1/7 eligible included in the clinical review for this comparison). The PARTNER-A and -B trials only use the Edwards SAPIEN valve, generalisability to other valves may be limited. Clinical event rates for (stroke, myocardial infarction and kidney injury) were assumed to remain constant after year 1 of the model due to a lack of data. Rates of temporary and permanent dialysis were also assumed to be the same for all 4 treatments due to a lack of data.				
Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations				

Abbreviations: AS: aortic stenosis; CI: confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost effectiveness ratio; NR= not reported; NYHA: New York Heart Association; QALYs= quality-adjusted life years; SAVR: surgical aortic valve replacement; RCT: randomised controlled trial; TAVI: transcatheter aortic valve implantation; TA: transapical; TF: transfemoral

(e) 'Cannot undergo surgery' defined as those with coexisting conditions associated with a predicted probability of ≥50% of death after surgery or a serious irreversible condition

(f) High risk defined as patients with a predicted risk of operative mortality of ≥15%or a society of Thoracic Surgery risk score of ≥10%

(g) Directly applicable / Partially applicable / Not applicable

(h) Minor limitations / Potentially serious limitations / Very serious limitation

Inoperable/intermediate risk

Study	Kodera 2018[200]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (decision tree and Markov model) **Approach to analysis:** Markov model with health states including Study entry, Hospitalisation (covering stroke, myocardial infarction and major vascular complications), Stability and Death. The model was run for inoperable and intermediate operative risk cohorts **Perspective:** Japanese healthcare **Time horizon:** 10-years **Discounting:** Costs: 2%; Outcomes: 2%	**Population:** People with severe AS who are cannot undergo surgery[(a)] and People with severe AS who have an intermediate risk of surgical complications[(b)] **Inoperable cohort settings:** Start age: 83 Male: 46% **Intermediate risk cohort settings:** Start age: 82 Male: 55% **Inoperable:** **Intervention 1** Medical therapy **Intervention 2:** TA or TF transcatheter aortic valve implantation (TAVI) **Intermediate risk:** **Intervention 1** Surgical aortic valve replacement (SAVR) **Intervention 2:** TF Transcatheter aortic valve implantation (TAVI)	**Inoperable total costs (mean per patient):** Intervention 1: £11,161 Intervention 2: £54,552 Incremental (2−1): Intervention 2 costs £43,391 more per person (95% CI: NR) **Intermediate risk total costs (mean per patient):** Intervention 1: £42,990 Intervention 2: £54,721 Incremental (2−1): Intervention 2 costs £11,731 more per person (95% CI: NR) **Currency & cost year:** 2016 Japanese Yen presented here as 2016 GBP (£) **Cost components incorporated:** Procedural costs, hospitalisation, drug costs and procedural complications (stroke, myocardial infarction and major vascular complications) and follow up costs.	**Inoperable QALYs (mean per patient):** Intervention 1: 1.27 Intervention 2: 3.02 Incremental (2−1): Intervention 2 gives 1.75 more QALYs (95% CI: NR) **Intermediate risk QALYs (mean per patient):** Intervention 1: 4.59 Intervention 2: 4.81 Incremental (2−1): Intervention 2 gives 0.22 more QALYs (95% CI: NR)	**Inoperable cohort ICER:** TA or TF-TAVI costs £26,673 per QALY gained compared to medical therapy **Intermediate risk cohort ICER:** TF-TAVI costs £51,210 per QALY gained compared to medical therapy **Analysis of uncertainty:** Deterministic sensitivity analyses showed that both models were sensitive to the 1 year mortality rate of TAVI and the cost of the TAVI procedure. TAVI was cost effective for the intermediate operative risk cohort when a 20-year time horizon was used. Probabilistic sensitivity analyses showed that intervention 2 had a 0.60 and 0.46 probability of being cost effective at a threshold of £34,032 per QALY gained in the inoperable and intermediate operative risk, respectively.
Data sources				

Health outcomes: A single RCT (PARTNER 2A) trial was used to inform the treatment effect for the TAVI vs SAVR cohort (1/7 eligible RCTs included in the clinical review). Mortality was partly informed by registry data (OCEAN TAVI Registry) **Quality-of-life weights**: EQ-5D **Cost sources:** Complication costs, follow up and procedural costs were taken from the literature. TAVI costs were obtained from the OCEAN TAVI Registry.	
Comments	
Source of funding: no funding was received **Limitations:** The PARTNER-A trial only uses the Edwards SAPIEN valve so generalisability to other valves may be limited. A single RCT (PARTNER-2A) trial was used to inform treatment effect for TAVI versus SAVR (1/7 eligible included in the clinical review for this comparison). The PARTNER- 2A trial only uses the Edwards SAPIEN XT valve so generalisability to other valves may be limited. The methodology used for discounting is unclear and the discount rate applied is 2% (instead of 3.5%). Probabilistic sensitivity analysis conducted using a threshold above the £30,000 threshold recommended in the NICE Reference Case. Mortality partly informed by observational data.	
Overall applicability:[(c)] Partially applicable	**Overall quality:**[(d)] Potentially serious limitations

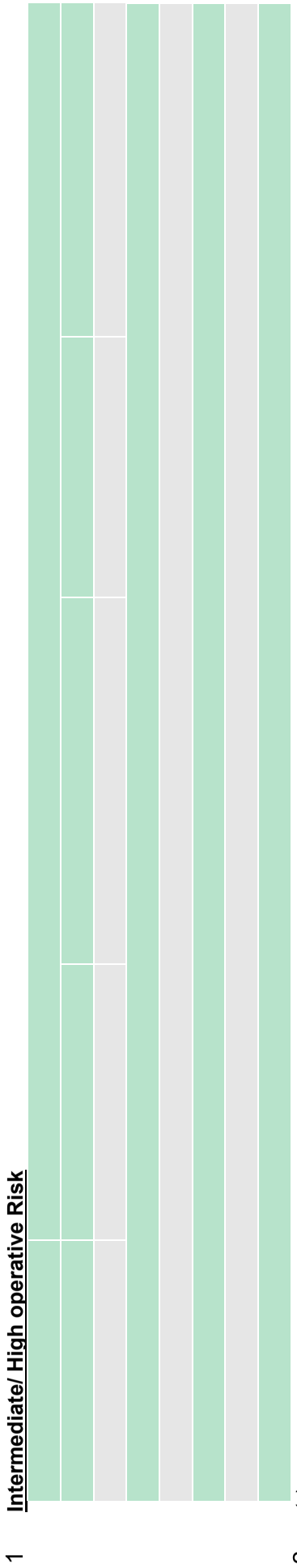
Abbreviations: AS: aortic stenosis; CI: confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years; SAVR: surgical aortic valve replacement; RCT: randomised controlled trial; TAVI: transcatheter aortic valve implantation; TA: transapical; TF: transfemoral

(a) 'Cannot undergo surgery' defined as those with coexisting conditions associated with a predicted probability of ≥50% of death after surgery or a serious irreversible condition

(b) Intermediate operative risk defined as those who have a STS risk score of >4% and<8%

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitation



Study	Tarride 2019[386]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility (health outcome: QALY) **Study design:** Decision analytic model (Markov model) **Approach to analysis:** Markov model with monthly cycles and several states according to the NYHA classification and on whether the patient experienced a stroke. **Perspective:** Canadian healthcare **Time horizon:** 15 years **Discounting:** Costs: 1.5%; Outcomes: 1.5%	**Population:** Patients with severe aortic stenosis undergoing SAVR or TAVI with intermediate or high operative risk **Cohort settings:** Start age: NR Male: NR **Intervention 1:** SAVR, surgical aortic valve replacement **Intervention 2:** TAVI, transcatheter aortic valve implantation	**High risk total costs (mean per patient):** Intervention 1: £42,473 Intervention 2: £46,535 Incremental (2−1): £4,062 (95% CI: NR; p=NR) **Intermediate risk total costs (mean per patient):** Intervention 1: £31,493 Intervention 2: £38,926 Incremental (2−1): £7,433 (95% CI: NR; p=NR) **Currency & cost year:** Canadian dollars (presented here as 2018 UK pounds) **Cost components incorporated:** Cost of the device, post-procedural inpatient costs, physician fees related to the procedure and to specialist consultations during the inpatient stay, along with workup costs that occurred in an emergency room or ambulatory setting just prior to admission and cost of medicines.	**High risk QALYs (mean per patient):** Intervention 1: 3.15 Intervention 2: 3.57 Incremental (2−1): 0.43 (95% CI: NR; p=NR) **Intermediate risk QALYs (mean per patient):** Intervention 1: 4.62 Intervention 2: 5.1 Incremental (2−1): 0.48 (95% CI: NR; p=NR)	**High risk ICER (Intervention 2 versus Intervention 1):** £9,510 per QALY gained (pa) 95% CI: Probability Intervention 2 cost effective (£27,585K/55,170K threshold): 93%/99% **Intermediate risk ICER (Intervention 2 versus Intervention 1):** £15,533 per QALY gained (pa) 95% CI: Probability Intervention 2 cost effective (£27,585K/55,170K threshold): 91%/99% **Analysis of uncertainty:** Probabilistic sensitivity analysis presented in the form of a cost-effectiveness results. It appears from the graph that at a threshold of $20,000, the probability that TAVI is cost-effective in high risk patients is above 90% whereas it is around 70% in the intermediate risk group. A number of deterministic sensitivity analyses were conducted. These are: use a time-horizon of 10 and 5 year; use different discounting rates (0, 3%); base initial hospitalisation cost on all patients independent of risk level; vary the cost of SAVR; exclude non-stroke management; increase and decrease the non-device procedure cost and include event disabilities. The results were found to be very sensitivity to the time-horizon assumed as the ICER of the intermediate-risk population became higher than the Canadian threshold of £27,585 when the time horizon of the model was reduced to 5 years.
Data sources				

Health outcomes: Health outcomes come from 3 sources of data. PARTNER IA study for SAVR high-risk population; PARTNER IIA for SAVR intermediate-risk population; and PARTNER II for TAVI intermediate- and high-risk population. Mortality beyond follow-up was extrapolated using a Weibull distribution whereas extrapolation for the other clinical events included was based on the last observed data **Quality-of-life weights:** EQ5D-3L data collected from PARTNER studies and valued using the Canadian EQ5D-3L algorithm. **Cost sources:** The cost of TAVI device was based on manufactures list price whereas the cost of SAVR was derived from a Canadian cost-effectiveness analysis. Other costs (e.g. hospitalisation) were calculated using unpublished patient level data from the Canadian Institute of Health Information (CIHI). Physician fees were based on expert opinion and the Ontario Schedule of Benefits for Physician Services.	
Comments	
Source of funding: Edwards Lifesciences. **Limitations:** Several outcomes included but only a few modelled as Markov states even though some of those have important implication on quality of life and mortality. Data from PARTNER I and PARTNER II, not a systematic review. Reintervention was not modelled despite available data indicates that it tends to occur earlier with TAVI. Mortality and clinical evidence based on non-randomized data. Cost data not adjusted for differences in baseline and subject to the peculiarities of patients undergoing SAVR or TAVI. **Other:**	
Overall applicability:[c] Partially applicable	**Overall quality:**[d] Potentially serious limitation

Abbreviations: CC= cost–comparison; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; TAVI= Transcatheter Aortic Valve Implantation; SAVR= Surgical aortic valve replacement.
(a) Converted using 2015 purchasing power parities[281]
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Intermediate operative risk

Study	**Goodall 2019[142]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (Markov model) **Approach to analysis:** Markov model with 9 heath states: NYHA classes I-IV with or without a history of stroke and death.	**Population:** People with severe AS who have an intermediate risk of surgery. Intermediate risk of surgery is defined as those who have a STS risk score of >4% and <8% **Cohort settings intervention 1 and**	**Total costs (mean per patient):** Intervention 1: £30,414 Intervention 2: £30,028 Incremental (2−1): Intervention 2 saves £386 per person (95% CI: NR) **Currency & cost year:** 2016 Euros presented here as 2016 GBP (£) **Cost components incorporated:** Index admission costs for TAVI and SAVR. Cost of the TAVI device was	**QALYs (mean per patient):** Intervention 1: 3.65 Intervention 2: 4.06 Incremental (2−1): Intervention 2 gives 0.41 more QALYs per person (95% CI: NR)	**TAVI dominates SAVR** **Analysis of uncertainty:** Deterministic sensitivity analyses for conducted for time horizon, discount rate, index admission cost and rehospitalisations. Results were robust to these analyses. A probabilistic sensitivity analysis showed that in 100% of simulations TAVI fell below a

Perspective: French healthcare **Time horizon:** 15- year **Discounting:** Costs: 4.0%; Outcomes:4.0%	**intervention 2:** Start age: 81.7 and 81.5 Male: 54.8% and 54.2% **Intervention 1:** Surgical aortic valve replacement (SAVR) **Intervention 2:** Transcatheter aortic valve implantation (TAVI)	added to this separately. Cardiac rehabilitation, hospitalisations, reintervention and adverse events (major stroke, TIA. Major bleeding, major vascular complication, atrial fibrillation, renal replacement therapy, myocardial infarction, endocarditis, pacemaker implantation.		threshold £13,200 per QALY gained compared to SAVR
Data sources				
Health outcomes: A single RCT (PARTNER-2) trial was used to inform treatment effect (1/7 eligible included in the clinical review), however, where parameters were not available from PARTNER-2 data from an observational (propensity score matched) study was used **Quality-of-life weights**: EQ-5D **Cost sources:** costs for TAVI, SAVR and adverse events (excluding stroke) were obtained from 2013 Programme de Medicalisation des Systemes d'Information. The cost of a stroke was taken from published literature.				
Comments				
Source of funding: funding provided by Edwards Lifesciences. **Limitations:** Observational data was used to inform health outcomes where RCT data was not available. A discount rate of 4.0% was applied to costs and health outcomes (instead of 3.5% as per NICE reference case).				
Overall applicability:[(a)] Partially applicable **Overall quality:**[(b)] Potentially serious limitations				

Abbreviations: AS: aortic stenosis; CI: confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); MM: medical management; NR= not reported; NYHA: New York Heart Association; PSSRU: Personal Social Services Research Unit; QALYs= quality-adjusted life years; RCT: randomised controlled trial; STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation; TIA: transient ischaemic attack;

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitation

Study	Tam 2018A [382]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (Markov model) **Approach to analysis:** Markov model with 5 heath states: After the procedural state, the cohort could transition between Disabling stroke, Alive/well, Dialysis and Dead. **Perspective:** Canadian healthcare **Time horizon:** 15- year **Discounting:** Costs: 1.5%; Outcomes:1.5%	**Population:** People with severe AS who have an intermediate risk of surgery. Intermediate risk of surgery is defined as those who have a STS risk score of >4% and <8%. **Cohort settings intervention 1 and intervention 2:** Start age: 81.7 and 81.5 Male: 54.8% and 54.2% **Intervention 1:** Surgical aortic valve replacement (SAVR) **Intervention 2:** Balloon expandable Transcatheter aortic valve implantation (TAVI)	**Total costs (mean per patient):** Intervention 1: £20,398 Intervention 2: £26,317 Incremental (2−1): Intervention 2 costs £5,919 more per person (95% CI: NR) **Currency & cost year:** 2016 Canadian dollars presented here as 2016 GBP (£) **Cost components incorporated:** Procedure costs (Valve, ward stay, ICU stay, staff, anaesthesia, insertion of temporary pacemaker wire, angiogram, angioplasty, and catheterisation). Long term costs (disabling and non-disabling stroke, hospitalisation, major bleeding, vascular injury, acute kidney injury, atrial fibrillation.	**QALYs (mean per patient):** Intervention 1: 5.40 Intervention 2: 5.63 Incremental (2−1): Intervention 2 gives 0.23 more QALYs per person (95% CI: NR)	**ICER (TAVI versus SAVR):** £25,856 per QALY gained (95% CI: £) **Analysis of uncertainty:** A probabilistic sensitivity analysis showed that in 52.7% of simulations TAVI fell below a threshold £28,000 per QALY gained compared to SAVR. A series of deterministic sensitivity analyses found that it was most sensitive to the cost of the TAVI valve system, length TAVI ICU stay and the peri-procedural mortality rate of TAVI and SAVR.
Data sources				
Health outcomes: A single RCT (PARTNER-2) trial was used to inform treatment effect (1/7 eligible included in the clinical review). The proportion of patients with acute kidney injury progressing to dialysis was not provided in the PARTNER-2 trial so was obtained from the PARTNER-1A trial. Published literature was used to estimate the probabilities of death during a long-term dialysis and of death patients with long-term strokes. **Quality-of-life weights**: EQ-5D **Cost sources:** Up front procedural costs were obtained from the Ontario Schedule of Benefits. Ward stay and ICU costs obtained from an Ontario based hospital. Costs of the TAVI valve system and surgical valve taken from the manufacturer, Edwards Lifesciences. Costs for peri-procedural complications were obtained from the 2014 Canadian Institute for Health Information Patient Cost Estimator Case Mix Group for those aged more than 80 years in Ontario. Stroke costs obtained from published literature.				

Comments
Source of funding: NR although authors declared conflicts of interest having financial relationships with Edwards Lifesciences and Medtronic. **Limitations:** A single RCT (PARTNER-2) trial was used to inform treatment effect (1/7 eligible included in the clinical review). The proportion of patients with acute kidney injury progressing to dialysis was not provided in the PARTNER 2 Trial and was estimated from the PARTNER 1A trial that used a different valve. Some observational data was used to inform health outcomes where RCT data was not available. A discount rate of 1.5% was applied to costs and health outcomes (instead of 3.5% as per NICE reference case).
Overall applicability:[a] Partially applicable **Overall quality:**[b] Potentially serious limitations

Abbreviations: AS: aortic stenosis; CI: confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death);GBP: Great British pound; ICU: intensive care unit; NR= not reported; PSSRU: QALYs= quality-adjusted life years; RCT: randomised controlled trial; SAVR: surgical aortic valve replacement; STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation; TIA: transient ischaemic attack;

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitation

Study	Tam 2018B [383]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (Markov model) **Approach to analysis:** Markov model with 5 heath states: After the procedural state, the cohort could transition between Disabling stroke, Alive/well, Dialysis and Dead. **Perspective:** Canadian healthcare **Time horizon:** Lifetime **Discounting:** Costs: 1.5%; Outcomes:1.5%	**Population:** People with severe AS who have an intermediate risk of surgery. **Cohort settings:** Mean TAVI and SAVR start age: 79.9 and 79.8. Mean TAVI and SAVR STS score: 4.4 and 4.5 Male: NR **Intervention 1:** Surgical aortic valve replacement (SAVR) **Intervention 2:** Self-expandable Transcatheter aortic valve implantation (TAVI)	**Total costs (mean per patient):** Intervention 1: £18,152 Intervention 2: £24,855 Incremental (2−1): Intervention 2 costs £6,343 more per person (95% CI: NR) **Currency & cost year:** 2016 Canadian dollars presented here as 2016 GBP (£) **Cost components incorporated:** Procedure costs (Valve, ward stay, ICU stay, staff, anaesthesia, insertion of temporary pacemaker wire, angiogram, angioplasty, and catheterisation). Peri-procedural complications. Long term disabling and non-disabling stroke.	**QALYs (mean per patient):** Intervention 1: 6.28 Intervention 2: 6.42 Incremental (2−1): Intervention 2 gives 0.15 more QALYs per person (95% CI: NR)	**ICER (TAVI versus SAVR):** £43,055 per QALY gained (95% CI: NR) **Analysis of uncertainty:** A probabilistic sensitivity analysis showed that in 52.9% of simulations TAVI fell below a threshold £28,000 per QALY gained compared to SAVR. A series of deterministic sensitivity analyses showed that the results were most sensitive to the cost of the TAVI valve and both TAVI and SAVR 30 day mortality.
Data sources				
Health outcomes: A single RCT (SURTAVI) trial was used to inform treatment effect (1/7 eligible included in the clinical review). **Quality-of-life weights**: EQ-5D **Cost sources:** Up front procedural costs were obtained from the Ontario Schedule of Benefits. Ward stay and ICU costs obtained from an Ontario based hospital. Costs of the TAVI valve system and surgical valve taken from the manufacturer, Medtronics Inc. Costs for peri-procedural complications were obtained from the 2014 Canadian Institute for Health Information Patient Cost Estimator Case Mix Group for those aged more than 80 years in Ontario. Stroke costs obtained from published literature.				
Comments				
Source of funding: NR although authors declared conflicts of interest having financial relationships with Edwards Lifesciences and Medtronic. **Limitations:** A single RCT (SURTAVI) trial was used to inform treatment effect (1/7 eligible included in the clinical review). utility data was obtained from an RCT (CoreValve trial) that looked at patients who were if high risk (as opposed to intermediate risk). A discount rate of 1.5% was applied to costs and health outcomes (instead of 3.5% as per NICE reference case).				
Overall applicability:[(a)] Partially applicable		**Overall quality:**[(b)] Potentially serious limitations		

Abbreviations: AS: aortic stenosis; CI: confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GBP: Great British pound; ICU: intensive care unit; NR= not reported; PSSRU: QALYs= quality-adjusted life years; RCT: randomised controlled trial; SAVR: surgical aortic valve replacement; STS: Society of Thoracic Surgeons; SURTAVI: Surgical Replacement and Transcatheter Aortic Valve Implantation trial; TAVI: transcatheter aortic valve implantation

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitation

Low operative risk

Study	**Tam 2020**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** **Approach to analysis:** A probabilistic Markov cohort model with 30 days cycle length, with 4 long-term health states after 30-days post procedure. **Perspective:** Canadian third-party payers' perspective **Time horizon/Follow-up**: lifetime **Discounting:** Costs: 1.5%; Outcomes: 1.5%	**Population:** Patients at low surgical risk with severe symptomatic aortic stenosis undergoing balloon expandable TAVI, self-expandable TAVI and SAVR. **Cohort settings:** Start age: 74 years old based on the 2 trials used Male: NR **Intervention 1:** Balloon-expandable TAVI **Intervention 2:** Self-expandable TAVI **Intervention 3:** SAVR	**Total costs (mean per patient):** Intervention 1: £21,260 Intervention 2: £22,587 Intervention 3: £19,670 Incremental (1-3): £1,590 Incremental (2-3): £ 2,917 (95% CI: NR; p=NR) **Currency & cost year:** 2019 Canadian dollars (presented here as 2019 UK pounds[(b)]) **Cost components incorporated:** Upfront procedural costs (TAVI systems, valve, cardiology fees, surgeon fees, surgical assistant fees, anaesthesiologist fee, ward and ICU stay).	**QALYs (mean per patient):** Intervention 1: 9.15 Intervention 2: 9.13 Intervention 3: 9.05 Incremental (1-3): 0.1 Incremental (2-3): 0.08 (95% CI: NR; p=NR)	**ICER (Intervention 1 versus Intervention 3):** £15,900 per QALY gained (pa) 95% CI: Probability Intervention 2 cost effective (£20K/30K threshold): XX%/XX% **ICER (Intervention 2 versus Intervention 3):** £36,463 per QALY gained (pa) **Analysis of uncertainty:** As the rates of complications were different in the SAVR arm of the 2 trials and a weighted mean event rates was used in the base case. A sensitivity analysis was conducted to examine the impact of using baseline complications rates for the SAVR arm for each of the individual trials rather than a mean of the two. Conclusion, the cost-effectiveness was impacted by baseline rates of

				complications in the clinical trials, the ICER when PARTNER 3 data was used; **ICER (Intervention 1 versus Intervention 3):** £38,118 per QALY gained (pa) **ICER (Intervention 2 versus Intervention 3):** £57,581 per QALY gained (pa) ICER when Evolut trial was used; **ICER (Intervention 1 versus Intervention 3):** Dominant **ICER (Intervention 2 versus Intervention 3):** £14,717 per QALY gained (pa) CEAC was conducted.

Data sources

Health outcomes: Health outcomes come from 2 sources of data. PARTNER 3 study for low risk patients and the Evolut Low Risk Trial. No direct clinical trials comparing balloon-expandable TAVI vs self-expandable vs SAVR in the low risk patients exists therefore a random-effects frequentist network meta-analysis with the PARTNER 3 and Evolut data, to get risk ratios or mean differences compared with SAVR. Mortality after 1 year was based on age- and gender- specific Canadian life tables given the absence of clinical data and the Partner 3 and Evolut trial follow-up. **Quality-of-life weights:** EuroQol (EQ5D) data collected from PARTNER 2 trials. Utilities for long term Markov states were estimated from literature for hospitalisation and studies and disabling stroke. Disutilities were estimated from observational studies of TAVI and SAVR patients published in the literature for major bleeding, vascular complications, atrial fibrillation, new pacemaker and non-disabling stroke. Disutility for hospitalisation was from a French cost-effectiveness model of patients with atrial fibrillation. **Cost sources:** The cost of TAVI systems and valve were based on manufactures list price, Edward Life Sciences and Medtronic Inc. The costs for peri-procedural complications were obtained from the 2014 Canadian Institute for Health Information patient Cost Estimator Case Mix Group for 60-79-year olds in Ontario. Cost for ward and ICU stays were used from previously published literature. Costs for long-term complication states were estimated from literature. Length of procedural, hospitals stay and ICY were obtained from the Partner 3 and Evolut trials.

Comments

Source of funding: H.C.W. received research grants from Medtronic Inc. and Edwards Lifesciences. J.C. received speaker Honoria from Edwards Lifesciences. **Limitations:** Non-UK perspective and not systematic review. The calculated incremental costs and QALYs vary from the reported ones, the

ones presented here in the table are the calculated ICER. Third party payer perspective. Non-UK study. Limited sensitivity analysis. As the sources used where for older population with a mean age of 74 years the results may not be generalisable to younger populations. **Other:**

Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; TAVI= Transcatheter aortic valve implantation; SAVR= Surgical aortic valve replacement

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

H.2 Aortic stenosis (bicuspid)

No evidence was found

H.3 Aortic stenosis (mixed non-bicuspid and bicuspid or unclear)

No evidence was found

H.4 Aortic regurgitation (non-bicuspid)

No evidence was found.

H.5 Aortic regurgitation (bicuspid)

No evidence was found.

H.6 Aortic regurgitation (mixed non-bicuspid and bicuspid or unclear)

No evidence was found

H.7 Mixed/unclear aortic valve disease

Study	Nair 2018[263]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Within-trial **Approach to analysis:** Resource use and HRQoL measured for all participants in the Mini-Stern Trial (RCT). HRQoL was adjusted for using multiple linear regression **Perspective:** UK NHS **Time horizon:** 12-months **Discounting:** Costs: N/A; Outcomes: N/A	**Population:** Adult patients undergoing first-time isolated AVR were included **Cohort characteristics for Intervention 1 and 2:** Sample size (n): 104 and 118 Start age: 72.1 and 71.3. Male: 45% and 55% **Intervention 1:** Full median sternotomy **Intervention 2:** Mini-sternotomy	**Total costs (mean per patient):** Intervention 1: £10,620 Intervention 2: £12,333 Incremental (2−1): Intervention 2 costs £2,154 more per person (95% CI: £2,083, £2,225) **Currency & cost year:** 2015 GBP (£) **Cost components incorporated:** Primary admission (theatre use, surgical items, critical care, cardiac ward, physio- and occupational therapy, rehabilitation, acute hospital). Post initial stay costs (hospital re-admission, follow up tests, follow up healthcare visits, drugs)	**QALYs (mean per patient):** Intervention 1: unclear Intervention 2: unclear Incremental (2−1): Intervention 2 gives 0.0122 less QALYs per person (95% CI: -0.0138, -0.0106)	**Full median sternotomy dominates mini-sternotomy** **Analysis of uncertainty:** Deterministic analyses showed that the results were robust (mini-sternotomy was either dominated or had an ICER above £30,000 per QALY) for all analyses apart from for a complete case analysis (ICER was £10,334 per QALY). A probabilistic sensitivity analysis showed that in 5.1% of simulations mini-sternotomy fell below a threshold £30,000 per QALY gained compared to full median sternotomy.
Data sources				
Health outcomes: Recorded from participants in the Mini-Stern trial **Quality-of-life weights**: EQ-5D UK tariff **Cost sources:** Staff costs were obtained from the PSSRU 2015, hospital costs were obtained from NHS Reference costs 2014-15, theatre use costs obtained from expert opinion, other costs obtained from published literature.				
Comments				
Source of funding: National Institute for Health Research (NIHR) **Limitations:** time horizon may be too short to draw conclusions about cost effectiveness over a lifetime, unclear what the adjusted QALY gain is for each intervention, intervention effect is estimated from a single RCT				
Overall applicability:[(a)] Directly applicable **Overall quality:**[(b)] Potentially serious limitations				

Abbreviations: CI: confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GBP: Great British pound; ICER: incremental cost effectiveness ratio; N/A= not applicable; PSSRU: Personal and Social Services Research Unit; QALYs= quality-adjusted life years; RCT: randomised controlled trial

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

H.8 Mitral stenosis

No evidence was found.

H.9 Mitral regurgitation

High-risk/inoperable

Study	Mealing 2013[246]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (Markov model) **Approach to analysis:** Two inter-linked Markov models; one short-term (30 days) and one long term (5 years). Health states included: Intervention, Within hospital care, Rehabilitation, Mitral valve surgery, Home and Death. **Perspective:** UK NHS **Time horizon:** 5 years	**Population:** Patients with severe mitral regurgitation ineligible for surgical intervention **Cohort settings:** Start age: NR Male: NR **Intervention 1:** Medical management **Intervention 2:** Percutaneous mitral valve repair	**Total costs (mean per patient):** Intervention 1: £4,610 Intervention 2: £31,156 Incremental (2−1): £26,989 (95% CI: £18,941-£38,660) **Currency & cost year:** 2011 GBP (£) **Cost components incorporated:** Drug costs, MitraClip delivery system, Hospitalisation costs including: ICU stay, non-ICU stay, stroke, cardiovascular surgery, myocardial infarction, renal failure, deep wound infection	**QALYs (mean per patient):** Intervention 1: 0.62 Intervention 2: 1.84 Incremental (2−1): 1.22 (95% CI: 1.17-1.27)	**ICER (Intervention 2 versus Intervention 1):** £22,153 per QALY gained (95% CI: £15,611 - £32,300) Probability percutaneous repair cost effective (£20K/30K threshold): 37%/93% **Analysis of uncertainty:** Probabilistic and deterministic sensitivity analyses were conducted. The deterministic analyses showed that the result was most sensitive to the time horizon used. When a time horizon was 10 years the ICER was £14,800 per QALY gained. The model was relatively to procedural, device costs and mortality.

Discounting: Costs: 3.5%; Outcomes: 3.5%				
Data sources				
Health outcomes: Treatment effect was informed by EVEREST II High Risk Registry and published literature. Heart failure hospitalisations for those receiving medical management was informed by a published literature search. Baseline HRQoL was taken as a gender-adjusted value representative of a UK population. A literature search was conducted to find utility decrements for those with MR, NYHA classes' I-IV, ICU stay, non-ICU stay, and treatment related adverse events. **Quality-of-life weights**: EQ-5D UK tariff **Cost sources:** Drug costs and other resource uses obtained from the BNF and NHS Reference Costs. Hospitalisation costs were calculated using weighted averages of the events (ICU, non-ICU, stroke, cardiovascular surgery, myocardial infarction, renal failure, and deep wound infection. Cost of the MitraClip delivery system was provided by Abbott. Estimates pf background medication were based upon expert opinion				
Comments				
Source of funding: funded through a consultancy agreement between Oxford Outcomes Ltd and Abbott Vascular. **Limitations:** Treatment effect was informed by the EVEREST II High Risk Registry, which is a prospective, single arm registry; it is non-randomised and therefore not included in the clinical review. Not all comparators available to this population were included in the study.				
Overall applicability:[(a)] Directly applicable		**Overall quality:**[(b)] Potentially serious limitations		

Abbreviations: BNF: British National Formulary; CI: confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HRQoL: health related quality of life; ICER= incremental cost-effectiveness ratio; ICU: intensive care unit; MR: mitral regurgitation; NR= not reported; NYHA: New York Heart Association; QALYs= quality-adjusted life years; RCT: randomised controlled trial

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Sakami 2019[327]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (Markov model) **Approach to analysis:** A Markov model consisting of two states: alive and death. People in the alive states are classified into 4 NYHA classes. The model	**Population:** Patients with symptomatic severe MR at high surgical risk **Cohort settings:** Start age: 74 Male: NR **Intervention 1:** Medical management	**Total costs (mean per patient):** Intervention 1: £32,348 Intervention 2: £51,906 Incremental (2−1): £19,558 (95% CI: NR) **Currency & cost year:** 2018 Japanese Yen presented here as 2018 GBP (£)	**QALYs (mean per patient):** Intervention 1: 2.43 Intervention 2: 3.85 Incremental (2−1): 1.42 (95% CI: NR)	**ICER (Intervention 2 versus Intervention 1):** £13,549 per QALY gained (95% CI: NR) Probability MitraClip cost effective (£34,415 threshold): 96.7% **Analysis of uncertainty:** Probabilistic and deterministic sensitivity analyses were conducted. The deterministic analyses showed that MitraClip ceases to be cost-

includes MitraClip complications, adverse events, reimplantation, MV surgery and CHF hospitalisation. **Perspective:** Japanese public healthcare payer **Time horizon:** Lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 2:** Transcatheter mitral valve repair with MitraClip device	**Cost components incorporated:** Device cost (MitraClip), technical fee, cost other than device cost and technical fee, MitraClip procedure hospitalisation, MV surgery, congestive heart failure hospitalisation, treatment cost for MitraClip complications (vascular complications, major bleeding, non-cerebral thromboembolism, drug cost, follow-up cost, adverse events costs (MI, stroke, renal failure, non-elective cardiovascular surgery, mechanical ventilation, GI complication requiring surgery, septicemia, blood transfusion).		effective when the HR for Overall Survival for MitraClip procedure against medical management exceeds 0.97. In addition, the incremental cost effectiveness ratio was found to be sensitive to the congestive heart failure hospitalisation rate for medical therapy and MitraClip. The probabilistic sensitivity analysis found only 3.3% of the simulations falling above the Japanese cost-effectiveness threshold of £34,415.

Data sources

Health outcomes: Treatment effect was informed by the study from Velazquez 2015 comparing patients treated with MitraClip with no-surgical treated patients using a propensity score matching approach. Likewise, data on NYHA class, re-implantation, MV surgery, hospitalisation, complication and adverse events were sought from Velazquez 2015 as well. Health utility scores and decrements were sought from the study from Cameron[69]. **Quality-of-life weights**: EQ-5D **Cost sources:** Cost of a MitraClip procedure comes from the Japanese Insurance Reimbursement for medical device and Medical Treatment Fee point April 2017. Drug costs were based on the prescription data of concomitant drugs in AVJ-514 trial. Outpatient follow-up cost was based on clinical expert's opinion. Unit costs for each resource usage were sought from the Medical Treatment Fee Point April 2017.

Comments

Source of funding: This study was funded by Abbott Vascular Japan Co., Ltd. **Limitations:** Treatment effect was not informed by a RCT but by 4 observational studies compared with a propensity score matching approach. The assumption that in the medical management arm no adverse event occur is disputable although conservative. Finally, for some key inputs such as resource use medical expert opinion was used instead of randomized or non-randomized data.

Overall applicability:[(a)] Partially applicable **Overall quality:**[(b)] Potentially serious limitations

Abbreviations: CI: confidence interval; CHF: congestive heart failure; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HRQoL: health related quality of life; ICER= incremental cost-effectiveness ratio; NR= not reported; NYHA: New York Heart Association; QALYs= quality-adjusted life years; RCT: randomised controlled trial
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Shore 2020[348]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model (Survival partition model) **Approach to analysis:** A survival partition model based on COAPT trial[367] consisting of two states: alive and death. People in the alive states are classified into 4 NYHA classes. The model includes clinical adverse events occurring 30 days after the procedure and hospitalization associated with NYHA. **Perspective:** UK NHS **Time horizon:** Lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** Patients with symptomatic severe functional MR at high surgical mortality or deemed inoperable. **Cohort settings:** Start age: 72 Male: 64% **Intervention 1:** Guideline directed medical therapy (GDMT) **Intervention 2:** Transcatheter mitral valve repair (TMVR) with MitraClip device + GDMT	**Total costs (mean per patient):** Intervention 1: £10,704 Intervention 2: £42,971 Incremental (2−1): £32,267 (95% CI: NR) **Currency & cost year:** 2020 GBP (£) **Cost components incorporated:** Device cost (MitraClip), pre-procedural cost, peri-procedural cost, cost of the initial hospital stay, rehabilitation cost, hospitalization cost, MV surgery and repeat MV intervention cost, background medication cost per month NYHA, outpatient care cost per month NYHA, replacement ICD/CRT cost,	**QALYs (mean per patient):** Intervention 1: 1.98 Intervention 2: 3.06 Incremental (2−1): 1.07 (95% CI: NR)	**ICER (Intervention 2 versus Intervention 1):** £30,057 per QALY gained (95% CI: NR) Probability MitraClip cost effective (£20k/£30k threshold): 0%/65% **Analysis of uncertainty:** Probabilistic and deterministic sensitivity analyses were conducted. The probabilistic sensitivity analysis indicates that MitraClip + GDMT has a 65% probability of being cost-effective at a threshold of £30,000. The deterministic sensitivity analysis showed that the model results are sensitive to the HR for mortality, rate of repeat MV intervention and MV surgery and to the cost of the procedure.

		cost of stroke, cost of MI, cost of heart transplant		

Data sources

Health outcomes: The study includes mortality extrapolated from COAPT, hospitalization rate based on the proportion of alive patients in each NYHA class, 30 day adverse events associated with GDMT and MitraClip. **Quality-of-life weights**: EQ-5D UK tariff **Cost sources:** NHS Reference Cost 2017/2018, NHS England, NICE guideline NG45, BNF and PSSRU.

Comments

Source of funding: This study funded by Edwards Lifesciences to develop the economic model and manuscript. **Limitations:** Treatment effect was derived by a single RCT rather than a systematic review. Some outcomes with potentially long-term consequences on survival, NHS resource use and QALYs were not modelled as long-term health states. The proportion of patients in each NYHA class was assumed to remain constant over the lifetime of the patients as no long-term data were available.

Overall applicability:[a] Partially applicable **Overall quality:**[b] Minor limitations

Abbreviations: CI: confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GDTM: Guideline directed medical therapy; HRQoL: health related quality of life; ICER= incremental cost-effectiveness ratio; TMVR: Transcatheter mitral valve repair; NR= not reported; NYHA: New York Heart Association; QALYs= quality-adjusted life years; RCT: randomised controlled trial

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

H.10 Mixed/unclear mitral valve disease

Study	Verbrugghe 2016 [408]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost comparison **Study design:** Retrospective cohort analysis with propensity score matching **Approach to analysis:** comparison of the hospital costs of different approaches to surgery for mitral valve disease in a single hospital **Perspective:** single Belgian hospital **Time horizon:** Initial inpatient stay **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** People who went isolated mitral valve surgery between 2004 and 2011 **Cohort characteristics intervention 1 and 2:** Mean age: 61 and 59 Male: 58% and 56% **Intervention 1:** Full median sternotomy **Intervention 2:** Minimally invasive surgery (port access)	**Total costs (mean per patient):** Intervention 1: £9,499 Intervention 2: £9,088 Incremental (2−1): £411 (95% CI: NR) **Currency & cost year:** 2010 Euros presented here as 2010 GBP (£) **Cost components incorporated:** Consultation, radiology, pathology, hospitalisation, ICU, operating room. These areas were broken down into write-down, pharmacy, medical staff, non-medical staff and operational cost.	**Occurrence of any complication:** Intervention 1: 61 (46.6%) Intervention 2: 34 (26.0%) Incremental (2−1): Intervention 2 had 27 (20.6%) less complications (95% CI: NR)	Minimally invasive surgery (port access) cost £411 less per person than full median sternotomy **Analysis of uncertainty:** No sensitivity analysis was conducted
Data sources				
Health outcomes: included mortality, any complication, reoperation, arrhythmia, neurologic complication, renal complication, pneumonia and wound infection. These were recorded from the participants in the retrospective cohort study**. Quality-of-life weights**: n/a **Cost sources:** financial department of University Hospitals Leuven				
Comments				
Source of funding: the study was supported by a research grant from Edwards Lifesciences **Limitations:** Cost of implants was excluded. Non-randomised retrospective analysis. Quality adjusted life years not used as an outcome. Sensitivity analyses not conducted				
Overall applicability:[(a)] Partially applicable **Overall quality:**[(b)] Potentially serious limitations				

Abbreviations: CI: confidence interval; ICU: intensive care unit; NR= not reported;

70. *(a) Directly applicable / Partially applicable / Not applicable(b) Minor limitations / Potentially serious limitations / Very serious limitations*

1 Appendix I: Excluded studies

I.1 Excluded clinical studies

3 **Table 62: Studies excluded from the clinical review**

Study	Exclusion reason
Afanasyev 2019[3]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Ailawadi 2019[5]	Incorrect study design
Ak 2018[6]	Inappropriate comparison
Akowuah 2017[7]	No relevant outcomes
Al Musa 2016[8]	Incorrect study design
Al otaibi 2017[9]	Systematic review is not relevant to review question or unclear PICO
Ali elbey 2019[10]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Amione-guerra 2018[11]	Not available for loan
Ando 2017[15]	Systematic review is not relevant to review question or unclear PICO. Systematic review: quality assessment is inadequate
Ando 2017[17]	Systematic review: quality assessment is inadequate
Ando 2019[16]	Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous
Ando 2019[14]	Systematic review: literature search not sufficiently rigorous. Systematic review is not relevant to review question or unclear PICO. Systematic review: quality assessment is inadequate. Underlying aortic valve disease type unclear
Ando 2019[13]	Systematic review: quality assessment is inadequate
Ansari 2015[18]	Systematic review: study designs inappropriate
Aris 1999[19]	Underlying aortic valve disease type unclear
Arnold 2013[26]	Unable to separate PARTNER cohorts so excluded to avoid double counting participants
Arnold 2014[24]	Unable to separate PARTNER cohorts so excluded to avoid double counting participants
Arora 2016[29]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Arora 2017[30]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Underlying aortic valve disease type unclear
Arora 2018[31]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Underlying aortic valve disease type unclear
Azraai 2020[34]	Systematic review is not relevant to review question or unclear PICO
Bail 2015[35]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Inappropriate comparison. Underlying mitral valve disease type unclear
Banovic 2016[36]	Protocol only - trial not yet complete
Barbero 2017[38]	Inappropriate comparison. Protocol only

Barili 2020[39]	Systematic review: methods are not adequate/unclear
Barker 2014[40]	Incorrect study design
Barros da silva 2020[46]	Systematic review: study designs inappropriate
Bates 2011[47]	Systematic review: study designs inappropriate
Bekeredjian 2013[48]	Not available - not in English
Ben farhat 1990[50]	Incorrect interventions
Benito-gonzalez 2020[51]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Bertaina 2019[53]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Biancari 2013[54]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Bing 2019[55]	Protocol only - trial not complete
Biondi-zoccai 2014[56]	Systematic review is not relevant to review question or unclear PICO
Bouhout 2017[62]	Not available for loan
Brown 2009[64]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Burke 2018[65]	Systematic review: methods are not adequate/unclear
Burrage 2017[66]	Systematic review: quality assessment is inadequate
Calafiore 2019[67]	Letter only. Incorrect interventions
Cao 2013[70]	Systematic review: quality assessment is inadequate
Cao 2013[71]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Underlying mitral valve disease type unclear
Cao 2016[72]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Cardoso 1998[75]	Not in English Language
Carnero-alcazar 2017[76]	Systematic review: quality assessment is inadequate. Systematic review is not relevant to review question or unclear PICO
Celik 2020[77]	Systematic review: study designs inappropriate. Systematic review is not relevant to review question or unclear PICO
Chang 2018[78]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Chateauneuf 2020[79]	Systematic review: study designs inappropriate
Chen 2018[80]	Not available for loan
Cheng 2011[82]	Systematic review: quality assessment is inadequate. Systematic review is not relevant to review question or unclear PICO
Conte 2016[84]	Incorrect study design
Cubero-gallego 2020[87]	Systematic review: quality assessment is inadequate
Daneault 2011[89]	Systematic review: methods are not adequate/unclear
Danielsen 2018[90]	Systematic review: study designs inappropriate
Daubert 2017[91]	Incorrect study design
David 1995[92]	Incorrect study design. Incorrect interventions. Inappropriate comparison
Dayan 2016[93]	Systematic review is not relevant to review question or unclear PICO
Dean 1994[94]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic

	review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Dewey 2013[96]	≥10% of one or more of the groups have had previous attempts at surgical or transcatheter management prior to the trial . Incorrect study design
Dhaliwal 2005[97]	Incorrect study design
Ding 2014[98]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Donato 2019[102]	Abstract only
Douglas 2017[104]	Incorrect study design
Dowling 2020[105]	Systematic review: quality assessment is inadequate
Dvir 2014[108]	Unable to separate PARTNER cohorts so excluded to avoid double counting participants
Elgendy 2019[111]	Correspondence only
Elmaraezy 2017[112]	Systematic review is not relevant to review question or unclear PICO
Eltchaninoff 2020[114]	Protocol only
Enezate 2017[115]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Falk 2011[117]	Incorrect study design
Fang 2019[118]	Systematic review is not relevant to review question or unclear PICO
Ferlini 2020[122]	Systematic review is not relevant to review question or unclear PICO
Ferrero guadagnoli 2018[123]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison
Figulla 2011[124]	Systematic review: study designs inappropriate
Forbes 2011[125]	Editorial
Fu 2019[126]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Gada 2015[127]	Unable to separate PARTNER cohorts so excluded to avoid double counting participants
Garg 2017[128]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Gargiulo 2016[129]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Ghanta 2016[133]	Incorrect study design
Giustino 2019[134]	Incorrect study design
Goel 2020[138]	Systematic review: study designs inappropriate
Gonzalez 2015[141]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Grabert 2016[143]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Underlying aortic valve disease type unclear
Grossi 1998[148]	Incorrect study design
Hamano 2001[152]	Patients have aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation with no clear majority and so cannot be stratified as per protocol

Hancock 2019[154]	No relevant outcomes
Hanedan 2017[155]	≥10% of one or more of the groups have had previous attempts at surgical or transcatheter management prior to the trial
Hauville 2012[157]	Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Health quality ontario 2016[158]	Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Herrmann 2013[160]	Unable to separate PARTNER cohorts so excluded to avoid double counting participants
Ho 2012[161]	Systematic review: quality assessment is inadequate
Hofer 2020[162]	Systematic review is not relevant to review question or unclear PICO
Hoffmann 2017[163]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Systematic review is not relevant to review question or unclear PICO
Holinski 2013[164]	No relevant outcomes
Hu 2011[165]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Indja 2020[168]	Incorrect study design
Indraratna 2016[169]	Systematic review: quality assessment is inadequate
Inoue 2020[170]	Incorrect study design
Jilaihawi 2012[172]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Jiritano 2019[173]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Juliard 2011[175]	Not available - not in English
Junquera 2019[176]	Systematic review: methods are not adequate/unclear. Systematic review: quality assessment is inadequate. Systematic review: literature search not sufficiently rigorous. Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate
Kang 2011[180]	Underlying type of mitral valve disease not stratafiable
Kapadia 2018[182]	Incorrect study design
Khan 2016[185]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Khan 2017[188]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Khan 2019[189]	Systematic review: quality assessment is inadequate
Khan 2020[187]	Systematic review: study designs inappropriate
Khan 2020[186]	Systematic review: quality assessment is inadequate
Kheiri 2019[190]	Systematic review: quality assessment is inadequate
Kheiri 2020[192]	Systematic review: quality assessment is inadequate. Systematic review is not relevant to review question or unclear PICO
Kheiri 2020[191]	Systematic review: quality assessment is inadequate
Khoshbin 2011[193]	Systematic review: quality assessment is inadequate
Kim 2014[194]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Kim 2014[195]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate

Kirklin 1991[196]	Letter
Kirmani 2017[197]	Systematic review is not relevant to review question or unclear PICO. Studies included have patients with aortic stenosis and aortic regurgitation with no clear majority and so cannot be stratified as per protocol
Kodali 2012[198]	Abstract only
Kolkailah 2019[202]	Systematic review is not relevant to review question or unclear PICO
Kolkailah 2019[201]	Protocol only
Kolte 2019[203]	Systematic review is not relevant to review question or unclear PICO
Koshy 2020[204]	Systematic review is not relevant to review question or unclear PICO
Kotronias 2020[205]	Systematic review is not relevant to review question or unclear PICO
Kuck 2016[206]	Not available - not in English
Kumar 2019[208]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Kumar 2020[207]	Systematic review: study designs inappropriate
Latif 2020[209]	Systematic review: study designs inappropriate
Lau 1997[210]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Laule 2019[211]	Letter only
Lazkani 2019[212]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Ler 2020[215]	Systematic review: methods are not adequate/unclear
Levett 2020[216]	Systematic review is not relevant to review question or unclear PICO
Lim 2015[218]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Underlying aortic valve disease type unclear
Lindqvist 2012[220]	Incorrect interventions
Liu 2018[222]	SR - only covers small proportion of population this review is interested in
Lloyd 2019[223]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Lodhi 2019[224]	Systematic review: methods are not adequate/unclear
Luo 2015[225]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Luthra 2020[226]	Systematic review: study designs inappropriate. Systematic review is not relevant to review question or unclear PICO
Lytvyn 2016[227]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Macedo 2018[228]	Incorrect study design
Malik 2020[237]	Systematic review is not relevant to review question or unclear PICO
Marmagkiolis 2019[238]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Martin gutierrez 2018[240]	Not available - not in English
Matsuda 2020[241]	Systematic review: study designs inappropriate

Mccarthy 2019[244]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Mcneely 2015[245]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Mihos 2016[248]	Incorrect study design
Mihos 2017[249]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Incorrect interventions
Mobinizadeh 2018[251]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Modi 2008[252]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Underlying aortic valve disease type unclear
Mohammadi 2016[253]	Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Systematic review: literature search not sufficiently rigorous
Mohananey 2018[254]	Systematic review: quality assessment is inadequate
Moore 2016[256]	Incorrect study design
Moscarelli 2020[257]	Systematic review: study designs inappropriate
Murtuza 2008[260]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Murtuza 2008[261]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Nagaraja 2014[262]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Nappi 2019[265]	Incorrect study design
Nappi 2020[264]	Systematic review: study designs inappropriate
Nemec 2012[268]	Incorrect study design
Nielsen 2012[271]	Systematic review: methods are not adequate/unclear. Systematic review: quality assessment is inadequate. Systematic review: literature search not sufficiently rigorous
Oldham 2018[276]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Olmos 1992[277]	Not in English language
Olmos 1994[278]	Not in English language
Olmos 1999[279]	Not in English language
Ontario 2020[280]	Systematic review is not relevant to review question or unclear PICO
Pagnesi 2017[283]	Article was a letter
Panchal 2013[284]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Panchal 2018[285]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Panoulas 2018[286]	Systematic review: quality assessment is inadequate
Patel 1991[288]	≥10% of one or more of the groups have had previous attempts at surgical or transcatheter management prior to the trial
Phan 2014[290]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate. Systematic review is not relevant to review question or unclear PICO
Phan 2015[291]	Systematic review: quality assessment is inadequate
Phankingthongkum 2002[292]	Incorrect study design. Inappropriate comparison

Philip 2014[293]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Pineda 2019[296]	Incorrect study design
Piriou 2019[297]	Protocol only
Polimeni 2020[298]	Systematic review is not relevant to review question or unclear PICO
Powell 2017[301]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Praz 2017[302]	Systematic review: methods are not adequate/unclear. Systematic review: quality assessment is inadequate
Qureshi 2018[303]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Raja 2009[304]	Systematic review is not relevant to review question or unclear PICO. Systematic review: quality assessment is inadequate
Rajani 2011[305]	Unable to separate PARTNER cohorts so excluded to avoid double counting participants
Rau 2012[306]	Incorrect study design. Inappropriate comparison
Rawasia 2020[307]	Systematic review is not relevant to review question or unclear PICO
Ren 2018[312]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Incorrect interventions. Inappropriate comparison
Richardson 2008[321]	Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Rodés-cabau 2014[323]	Unable to separate PARTNER cohorts so excluded to avoid double counting participants
Sa 2020[326]	Systematic review: study designs inappropriate
Salcher 2016[328]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Saleem 2019[329]	Systematic review is not relevant to review question or unclear PICO
Salmasi 2016[330]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Sansone 2012[331]	Incorrect study design
Santana 2017[332]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Incorrect interventions. Inappropriate comparison
Sardar 2017[334]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Saung 2019[335]	Adults with congenital heart disease (excluding bicuspid aortic valves). Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Sawa 1998[336]	Not available - not in English
Sechtem 2016[337]	Not available - not in English
Sehatzadeh 2013[339]	Systematic review: quality assessment is inadequate
Seiffert 2019[340]	Protocol only
Sergi 2019[341]	Systematic review: quality assessment is inadequate
Shah 2018[343]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate

Shah 2019[344]	Systematic review: quality assessment is inadequate
Shang 2016[345]	Adults with congenital heart disease (excluding bicuspid aortic valves). Article was a letter
Shehada 2018[346]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Shuhaiber 2007[349]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Siddiqui 2018[350]	Systematic review: quality assessment is inadequate
Siddiqui 2020[351]	Systematic review: quality assessment is inadequate
Siemieniuk 2016[352]	Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Singh 2018[354]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Singh 2020[353]	Systematic review is not relevant to review question or unclear PICO
Siontis 2016[356]	Systematic review: quality assessment is inadequate
Siontis 2019[355]	Systematic review: quality assessment is inadequate
Siordia 2018[357]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Skelding 2016[358]	Incorrect study design
Spertus 2019[363]	Incorrect study design
Stewart 2016[366]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Sultan 2010[368]	Inappropriate comparison. Systematic review: literature search not sufficiently rigorous. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Underlying tricuspid valve disease type unclear
Sundermann 2014[370]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Underlying mitral valve disease type unclear
Sundermann 2015[369]	Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Underlying mitral valve disease type unclear
Svensson 2013[372]	Unable to separate PARTNER cohorts so excluded to avoid double counting participants
Takagi 2013[378]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Takagi 2016[379]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Takagi 2016[380]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Takagi 2017[373]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Takagi 2017[374]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Takagi 2019[375]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate

Takagi 2020[377]	Systematic review: quality assessment is inadequate
Takagi 2020[376]	Systematic review is not relevant to review question or unclear PICO
Tam 2017[384]	Not available for loan
Tam 2020[381]	Incorrect study design
Tan 2017[385]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Tarus 2020[387]	Systematic review: study designs inappropriate
Thongprayoon 2015[388]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate. Systematic review is not relevant to review question or unclear PICO
Thourani 2015[389]	Unable to separate PARTNER cohorts so excluded to avoid double counting participants
Thyregod 2015[394]	Protocol only
Tietge 2012[395]	Protocol only
Tokmakoglu 2001[396]	Incorrect study design
Tsu 2017[397]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Tunerir 2005[398]	Underlying mitral valve disease type unclear
Ueshima 2019[400]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Ueshima 2019[401]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate. Systematic review is not relevant to review question or unclear PICO
Ueyama 2020[402]	Inappropriate comparison. Systematic review: methods are not adequate/unclear
Ullah 2020[403]	Systematic review: study designs inappropriate
Uva 2019[405]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Vendrik 2020[407]	Incorrect study design
Vilela 2015[409]	Article noting withdrawal of a Cochrane review protocol
Villablanca 2016[410]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Vipparthy 2020[411]	Systematic review is not relevant to review question or unclear PICO
Vohra 2013[412]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Wagner 2019[414]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Wan 2013[415]	Protocol only
Wang 2013[421]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Wang 2016[419]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Wang 2018[420]	Systematic review: quality assessment is inadequate
Wang 2018[418]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Wang 2020[417]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate

Wang 2020[416]	Systematic review: quality assessment is inadequate
Wijeysundera 2014[424]	Study design
Williams 2012[426]	Abstract only
Witberg 2018[427]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Witberg 2019[428]	Systematic review is not relevant to review question or unclear PICO
Wong 2019[430]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
You 2012[431]	Not available - not in English
Yun-dan 2017[432]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Zhang 2016[434]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Zhang 2020[433]	Systematic review is not relevant to review question or unclear PICO. Systematic review: quality assessment is inadequate
Zhang 2020[436]	Systematic review is not relevant to review question or unclear PICO
Zhang 2020[435]	Systematic review: methods are not adequate/unclear
Zhou 2017[437]	Systematic review: study designs inappropriate
Zimarino 2020[438]	Systematic review is not relevant to review question or unclear PICO

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 63: Studies excluded from the health economic review

Reference	Reason for exclusion
Armoiry 2018[21]	This cost consequence study was assessed as partially applicable (German setting may not reflect current NHS context). A more applicable UK cost utility analysis [116] was available that used the same comparators. Consequently, this study was selectively excluded.
Asgar 2017[33]	This study was assessed as partially applicable (Canadian setting may not reflect current NHS context). There are methodological limitations as it was based on observational data. Given that a more applicable UK analysis [246] was available that incorporated RCT data, this study was selectively excluded.
Beresniak 2013[52]	This study was assessed as having severe methodological limitations as it was a non-comparative study that used observational data.
Borisenko 2015[61]	This study was assessed as partially applicable (German setting may not reflect current NHS context). There are methodological limitations as it was based on observational data. Given that a more applicable UK analysis [246] was available that incorporated RCT data, this study was selectively excluded.
Brecker 2014[63]	This study was assessed as directly applicable (UK setting); however, given that a UK analyses [282] [422] [259] was available that was

Reference	Reason for exclusion
	based on RCT data (as opposed to observational data) this study was selectively excluded.
Cameron 2014[69]	This study was assessed as partially applicable (French setting may not reflect current NHS context). There are methodological limitations as it was based on observational data. Given that a more applicable UK analysis [246] was available that incorporated RCT data, this study was selectively excluded.
Cao 2016[72]	This study was excluded as it was excluded from the clinical review due to inadequate quality and inappropriate study design
Conradi 2015[83]	This cost comparison study was assessed as partially applicable (German setting may not reflect current NHS context). There are methodological limitations as it was based on observational data. Given that a more applicable UK analysis [246] was available that incorporated RCT data, this study was selectively excluded.
Fairbairn 2013[116]	This cost-utility analysis was excluded due to potentially serious methodological limitations. In particular, the source used to cost the intervention was assessed to be not reflective of the reality of the NHS as the estimated cost of a full TAVI intervention (£16,500) was found to be lower than the cost of the device alone (around £20,000 according to the NHS Supply Chain Catalogue)
Geisler 2017[131]	This study was assessed as partially applicable (Dutch setting may not reflect current NHS context). A more applicable UK analysis [116] was available that gave similar results (although different trial data was utilised). Consequently, this study was selectively excluded.
Guerin 2016[150]	This study was assessed as partially applicable (French setting may not reflect current NHS context). There are methodological limitations as it was based on observational data and does not utilise QALYs. Given that a more applicable UK analysis [246] was available that incorporated RCT data, this study was selectively excluded.
Huchet 2020[166]	This study was assessed as having severe methodological limitations as it reports that the operative risk is higher for TAVI but does not control for that difference.
Hancock-Howard 2013[153]	This cost utility analysis was assessed as partially applicable (Canadian setting may not reflect current NHS context). There are methodological limitations as it used a short 3 year time horizon. Given that a more applicable UK[259, 282, 422] and Canadian[99] analyses are available that use longer and more appropriate time horizons, this study was selectively excluded.
Health Quality Ontario 2016[158]	This cost utility analysis was assessed as partially applicable (Canadian setting may not reflect current NHS context). A more applicable UK cost utility analysis [116] was available that used the same comparators and reached the same conclusions that TAVI was cost effective. Consequently, this study was selectively excluded.
Huygens 2018 [167]	This cost comparison study was excluded due to limited applicability. Cost data was based on Dutch insurance claims for both mitral and aortic valve positions that are unlikely to reflect the UK NHS setting.
Kaier 2017[178]	This cost comparison study was assessed as partially applicable (single Italian hospital setting may not reflect current NHS context). A more applicable UK cost utility analysis [116] was available that used the same comparators. Consequently, this study was selectively excluded.
Kaier 2019[179]	This cost effectiveness analysis was excluded due to very serious limitations. The analysis only looked at hospital mortality which is

Reference	Reason for exclusion
	only one of the several relevant outcomes of interest. Furthermore, the outcome chosen is biased towards TAVI being cost-effective
Murphy 2013[259]	This cost-utility analysis was assessed as having very serious limitations. The reported life-years gained from the analysis were implausibly small, given that it was based on the PARTNER-1B trial. Two other included UK cost-utility analyses[282 422] reported more plausible QALY gains.
Neyt 2012[269]	This cost utility analysis was assessed as partially applicable (Belgian setting may not reflect current NHS context). More applicable UK cost utility analyses [116 282 422 259] were available that used the same RCT data. Consequently, this study was selectively excluded.
Povero 2018[300]	This study was assessed as partially applicable (included a UK setting amongst other countries); however, given that a UK analysis [116] was available that was based on RCT data (as opposed to observational data used for this study) this study was selectively excluded.
Ribera 2015[320]	This study was assessed as partially applicable (Spanish setting may not reflect current NHS context). There are methodological limitations as it was based on observational data. Given that more applicable analyses that incorporated RCT data were available [142, 382, 383], this study was selectively excluded.
Santarpino 2015[333]	This cost consequence study was assessed as partially applicable (German setting may not reflect current NHS context). A more applicable UK cost utility analysis [116] was available that used the same comparators. Consequently, this study was selectively excluded.
Sehatzadeh 2012[338]	This cost utility analysis was assessed as partially applicable (Canadian setting may not reflect current NHS context). A more applicable UK cost utility analysis [116] was available that used the same trial data (PARTNER-1B). The study reached the same conclusions. Consequently, this study was selectively excluded.
Sehatzadeh 2013[339]	This cost utility analysis was assessed as partially applicable (Canadian setting may not reflect current NHS context). More applicable UK cost utility analyses [116 282 422 259] were available that used the same RCT data. Consequently, this study was selectively excluded.
Sponga 2017[365]	This cost consequence study was assessed as partially applicable (single Italian hospital setting may not reflect current NHS context). A more applicable UK cost utility analysis [116] was available that used the same comparators. Consequently, this study was selectively excluded.
University of Glasgow[404]	This cost utility analysis was assessed as directly applicable (Scottish setting). However it utilised observational data. Other more recent UK cost utility analyses [116 282 422 259] that used RCT data are available. Consequently, this study was selectively excluded.
Wijeysundera 2016[423]	This cost consequence study was assessed as partially applicable (Canadian setting may not reflect current NHS context). A more applicable UK cost utility analysis [116] was available that used the same comparators. Consequently, this study was selectively excluded.

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Appendix J: Research recommendations

J.1 Interventions

J.1.1 Research recommendation

What is the most clinically and cost-effective management strategy for adults with calcific mitral stenosis and an indication for intervention?

J.1.2 Why this is important

This condition is predominantly associated with ageing and is therefore increasing in prevalence. Open surgery is technically difficult and carries a high risk.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Because of the high risk of serious complications and the technically difficult nature of the surgery, many of these patients are often turned down for operative treatment.
Relevance to NICE guidance	Treatment of calcific degenerative mitral stenosis was considered in this guideline; however, the randomised controlled trials identified for mitral stenosis all focused on rheumatic mitral stenosis rather than calcific degenerative mitral stenosis. As the pathophysiology and treatment options for these two types of mitral stenosis differ, recommendations made in this area were limited to rheumatic mitral stenosis and could not be extrapolated to cover calcific degenerative mitral stenosis. Answering this question could therefore allow recommendations to be made for calcific degenerative mitral stenosis as well as rheumatic mitral stenosis. NICE is currently unable to provide a recommendation for a condition that afflicts an increasing number of elderly patients. Evidence from new research may correct this.
Relevance to the NHS	Patients with this condition are often turned down for surgery. In the absence of evidence based alternative treatment, patients are treated conservatively/medically. Medical treatment of a structural problem is often ineffective and many of these patients endure repeated hospital admissions.
National priorities	Rollout of non-TAVI transcatheter treatments of heart valve disease.
Current evidence base	Although seven randomised controlled trials were included in the review for mitral stenosis, covering various comparisons, all of these focused on rheumatic mitral stenosis and not calcific degenerative mitral stenosis. Due to differences in pathophysiology and treatment

	options, this evidence was not appropriate to use to inform recommendations on calcific degenerative mitral stenosis and data from randomised controlled trials within this population is required to inform recommendations. Rheumatic mitral stenosis is a condition of predominantly younger female patients in low income countries. The evidence base for use of transcatheter treatments (namely balloon valvuloplasty) as well as open surgery (open commissurotomy or valve replacement) is strong. Mitral stenosis associated with MAC is a different disease affecting a different population of (elderly) patients. Treatments are technically difficult and apart from sparse individual case reports, not extensively studied
Equality considerations	This condition predominantly affects the elderly who often are assumed to be frail and therefore are unconsciously discriminated against.

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J.124 Modified PICO table

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Population	Inclusion Adults aged 18 years and over with diagnosed calcific degenerative mitral stenosis requiring their first intervention and suitable for surgery. Exclusion • Children (aged <18 years) • Those with one or more previous surgical or transcatheter interventions for calcific degenerative mitral stenosis • Those where surgery is not suitable • Adults with congenital heart disease (other than bicuspid aortic valves)
Intervention	Transcatheter mitral valve replacement (TMVR)
Comparator	Open surgery OR medical treatment .
Outcome	Primary outcomes All-cause mortality at ≥12 months; cardiac mortality at ≥12 months; intervention-related mortality at 30 days; health-related quality of life at ≥12 months; onset or exacerbation of heart failure at ≥12 months; intervention-related stroke or TIA at 30 days; intervention-related major bleeding at 30 days; need for re-intervention at ≥12 months Secondary outcomes

	Length of stay (following initial intervention); re-hospitalisation at ≥12 months; intervention-related pacemaker implantation at 30 days; intervention-related atrial fibrillation at 30 days; intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication); prosthetic valve endocarditis at ≥12 months
Study design	Randomised controlled trial
Timeframe	Long term (ideally >5 years follow-up)
Additional information	None

Research recommendation

What is the most clinically and cost-effective management strategy for adults with tricuspid regurgitation?

J.15 Why this is important

Severe tricuspid regurgitation is often referred for surgery late, when the right ventricle is severely dilated and has poor systolic function and the tricuspid valve subvalvular apparatus is significantly distorted. This results in high mortality and high likelihood of failure of tricuspid valve repair, and consequently further increases the reluctance to refer for surgery and to operate. It is important to determine the best management strategy – pharmacological management only, versus tricuspid valve surgical repair or replacement, versus tricuspid valve transcatheter repair.

J.16 Rationale for research recommendation

Importance to 'patients' or the population	Severe tricuspid regurgitation is often referred for surgery late, when the right ventricle is severely dilated and has poor systolic function and the tricuspid valve subvalvular apparatus is significantly distorted. This results in high mortality and high likelihood of failure of tricuspid valve repair, and consequently further increases the reluctance to refer for surgery and to operate. It is important to determine the best management strategy – pharmacological management only, versus tricuspid valve surgical repair or replacement, versus tricuspid valve transcatheter repair.
Relevance to NICE guidance	Treatment of tricuspid regurgitation was considered in this guideline; however, only a single, very small randomised controlled trial was identified and this could not be used to base recommendations on. Answering this question with larger randomised controlled trials may allow recommendations to be made for intervention in tricuspid regurgitation.
Relevance to the NHS	Implement novel techniques (transcatheter tricuspid valve repair) if evidence demonstrates them effective and cost effective

National priorities	National Service Framework: Coronary Heart Disease
Current evidence base	Only a single randomised controlled trial with 14 participants in each arm was identified comparing interventions in tricuspid regurgitation. This was insufficient to base recommendations on due to uncertainty for all outcomes reported and the extremely small size of the study. Data from larger randomised controlled trials within this population is required to inform recommendations within this population.
Equality considerations	None identified

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J.127 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed severe tricuspid regurgitation requiring their first intervention. Exclusion • Children (aged <18 years)
Intervention	Transcatheter repair Surgical tricuspid valve replacement 1. Median sternotomy replacement 2. Minimally invasive surgery replacement Surgical tricuspid valve repair 1. Median sternotomy repair2. Minimally invasive surgery repair
Comparator	Medical treatment Note: The focus of the question is surgical replacement or repair or transcatheter repair compared to each other and to medical treatment and therefore comparisons between minimally invasive and median sternotomy surgical replacement, or between minimally invasive and standard surgical repair, are not required.
Outcome	Primary outcomes All-cause mortality at ≥12 months; cardiac mortality at ≥12 months; intervention-related mortality at 30 days; health-related quality of life at ≥12 months; onset or exacerbation of heart failure at ≥12 months; intervention-related stroke or TIA at 30 days; intervention-related major bleeding at 30 days; need for re-intervention at ≥12 months Secondary outcomes

	Length of stay (following initial intervention); re-hospitalisation at ≥12 months; intervention-related pacemaker implantation at 30 days; intervention-related atrial fibrillation at 30 days;
Study design	Randomised controlled trial
Timeframe	Long term (ideally >5 years follow-up)
Additional information	None

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