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CADTH RAPID RESPONSE REPORT:
PEER-REVIEWED SUMMARY WITH CRITICAL APPRAISAL

Transcatheter Aortic Valve Implantation for Degenerated Mitral or Tricuspid Bioprostheses: A Review of Clinical Effectiveness and Cost-Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	October 2, 2020
Report Length:	50 Pages

CADTH

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Cite As: Transcatheter Aortic Valve Implantation for Degenerated Mitral or Tricuspid Bioprostheses: A Review of Clinical Effectiveness and Cost-Effectiveness. Ottawa: CADTH; 2020 Oct. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

aOR	Adjusted Odds Ratio
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
ICU	Intensive Care Unit
LCOS	Low Cardiac Output Syndrome
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MI	Myocardial Infarction
MIMVR	Mitral Valve Replacement Through Right Anterior Minithoracotomy
MVIV	Transcatheter Mitral Valve-in-Valve Implantation
NYHA	New York Heart Association
SD	Standard Deviation
SMVR	Surgical Mitral Valve Replacement
STS	Society of Thoracic Surgeons
TAVI	Transcatheter Aortic Valve Implantation
TMVR	Transcatheter Mitral Valve-In-Valve Replacement
TVIV	Transcatheter Tricuspid Valve-in-Valve Implantation
VIV	Valve-in-Valve

Context and Policy Issues

The prevalence of valvular heart disease is around 2.5% in industrialized countries.[1] Valvular heart disease can occur in any of the four valves in the heart (pulmonary, mitral, aortic, and/or tricuspid valve) and can involve stiffening of the valve (stenosis), prolapse, or leaking (regurgitation).[2] These diseases can be congenital (developing at or before birth) or acquired (e.g. due to degeneration with age or an infection).[2] Symptoms may vary according to the severity of damage to the valve and its function, and include chest pain or tightness, palpitations, shortness of breath, and fatigue, among others.[2]

In some patients, surgery may be required to repair or replace the heart valves.[2] One approach is to replace the damaged valve via open heart surgery, with a mechanical or biological valve (bioprosthesis).[2] An alternative approach, which is indicated and funded in Canada for the aortic valve, is to use a transcatheter procedure such as transcatheter aortic valve implantation (TAVI).[3] Here, the replacement valve is inserted using a catheter instead of via open heart surgery.[2] In recent years, transcatheter interventions have also been used off-label for tricuspid and mitral valves, where aortic valves are implanted in damaged tricuspid or mitral valves.[4] Among valvular heart disease interventions, those performed in

the aortic position are by far the most common, followed by procedures in the mitral position, then tricuspid position.[5]

In patients who initially received a mitral or tricuspid bioprosthesis, the bioprosthesis may degenerate over time, prompting consideration of additional repair or replacement. These patients can represent a challenge for further interventions in general, because they are often considered high risk for another surgery due to multiple co-morbidities or left ventricular dysfunction or pulmonary hypertension, or because there is limited evidence supporting surgical intervention of a degenerated mitral or tricuspid valve relative to medical management.[4,6-8] A less invasive approach such as transcatheter valve replacement, may be an attractive option in situations where there is a mitral or tricuspid bioprosthesis which has degenerated.[8] One approach is to insert an aortic valve in an existing degenerated mitral or tricuspid bioprosthesis using a catheter, which is termed a valve-in-valve (VIV or ViV) intervention.[4] The United States Food and Drug Administration approved use of the Edwards Sapien 3 valve for mitral VIV procedures in 2017, which is indicated "for patients with symptomatic heart disease due to failure of a previously placed bioprosthetic aortic or mitral valve whose risk of death or severe complications from repeat surgery is high or greater."[9] Health Canada also approved the Edwards Sapien 3 in 2019 for "symptomatic heart disease due to a failing mitral surgical bioprosthetic valve (stenosed, insufficient, or combined) who are judged by a heart team to be at high or greater risk for open surgical therapy."[10] However, there remains limited clinical experience with this technique and its use has been regarded as being at an early stage.[4] Therefore, it would be helpful to understand what evidence exists surrounding clinical effectiveness and cost-effectiveness of transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses. Such evidence would be useful in informing whether this technique can be more widely adopted in a Canadian context, or whether more research is needed to inform decision and policy-making.

The objective of this report is to summarize the evidence regarding the clinical effectiveness and cost-effectiveness of transcatheter aortic valve implantation for degenerated mitral or tricuspid bioprostheses.

Research Questions

1. What is the clinical effectiveness of transcatheter aortic valve implantation for degenerated mitral or tricuspid bioprostheses?
2. What is the cost-effectiveness of transcatheter aortic valve implantation for degenerated mitral or tricuspid bioprostheses?

Key Findings

Nineteen studies were retrieved surrounding the clinical effectiveness of transcatheter aortic valve implantation for patients with degenerated mitral or tricuspid valve bioprostheses, comprising one systematic review of single arm studies, two non-randomized studies with comparator groups, and 16 single-arm studies with no comparator groups.

Two retrospective cohort studies in patients with degenerated mitral valve bioprostheses reported no difference for in-hospital mortality, or mortality at one and two years, for transcatheter mitral valve-in-valve procedures compared to surgical replacement. One study also concluded that there was a trend towards improved clinical outcomes, such as

reduced rates of stroke and bleeding, for transcatheter procedures compared to surgical replacement; however, these differences were not statistically significant. There were serious limitations in both studies related to selection bias, bias due to confounding, and small sample size (121 patients in one study and 61 patients in the other study).

One systematic review and 12 single arm studies evaluated transcatheter valve-in-valve procedures for degenerated mitral valve bioprostheses in patients at high risk for surgery. Four single arm studies evaluated transcatheter valve-in-valve procedures for degenerated tricuspid valves in patients at high risk for surgery. Authors of these studies concluded, based on low rates of mortality, complications, and adverse effects, that transcatheter procedures were feasible, effective, and safe. New York Heart Association functional class improved after the procedure compared to baseline, suggesting that transcatheter valve-in-valve procedures for degenerated mitral or tricuspid valves lead to improved patient function and symptoms compared to baseline. These single arm studies were mostly small (11 out of 12 mitral valve studies had sample sizes ≤ 60 and three out of four tricuspid valve studies had sample sizes ≤ 7) and lacked comparison groups, making it impossible to judge the benefits and harms of transcatheter approaches relative to surgery or medical management. Authors of these studies acknowledged the need for larger, long-term studies.

No relevant economic evaluations were identified and thus the cost-effectiveness of transcatheter aortic valve implantation for degenerated mitral or tricuspid valves is unclear.

Despite identifying nineteen eligible studies for this report, the limitations and methodological concerns with current body of evidence suggest that further research is necessary to establish the clinical effectiveness and cost-effectiveness of transcatheter aortic valve implantation for degenerated mitral or tricuspid bioprostheses compared to open-heart surgical procedures and medical management. While it may be challenging or impossible to conduct randomized studies (given high or prohibitive risk for re-do surgery) or mitigate selection bias in this context, future studies of transcatheter aortic valve implantation for degenerated mitral or tricuspid valves should feature larger sample sizes, comparator groups, and appropriate techniques to minimize selection bias and bias due to confounding, particularly confounding by indication, in order to generate higher-quality evidence.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were TAVR or valve-in-valve replacement and degenerated mitral or tricuspid bioprostheses. Search filters were applied to limit retrieval to health technology assessments, systematic reviews (SR), meta-analyses, or network meta-analyses, randomized controlled trials, controlled clinical trials, or any other type of clinical trial (including single-arm studies), and economic studies. Where possible, retrieval was limited

to the human population. The search was also limited to English language documents published between January 1, 2015 and July 29, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients over 18 years old with degenerated mitral or tricuspid bioprostheses
Intervention	Transcatheter valve-in-valve replacement using a transcatheter aortic valve
Comparator	Second open-heart valve replacement surgery (replacing the original prosthetic valve or valve-in-valve), medical therapies, or before transcatheter valve-in-valve replacement using a transcatheter aortic valve
Outcomes	Q1: Clinical effectiveness (e.g., all-cause mortality, stroke, New York Heart Association Functional Class) Q2: Cost-effectiveness
Study Designs	Health technology assessments/systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies (including single-arm studies), economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Primary studies retrieved by the search were excluded if they were captured in one or more included SRs.

Critical Appraisal of Individual Studies

Eligible systematic reviews were critically appraised by one reviewer using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2).[11] Non-randomized studies were appraised using the Downs and Black checklist.[12] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 762 citations were identified in the literature search and one citation was retrieved from other sources. Following screening of titles and abstracts, 710 citations were excluded and 53 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 34 publications were excluded for various reasons, and 19 publications comprising one SR and 18 non-randomized studies met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[13] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One 2018 SR[14] was eligible. The search date was from 2000 (day and month not specified) to March 30, 2018. The SR had a broader scope than this report and reviewed outcomes of transcatheter mitral valve-in-valve implantation (MVIV) procedures for degenerated mitral valve bioprostheses and transcathether mitral valves for failed annuloplasty rings (valve-in-ring; TMVIR). There were 101 eligible studies in this SR and 66 studies were relevant to this report. All studies included in the SR were single arm studies.

A total of 18 non-randomized studies were identified. Two studies[15,16] were retrospective cohort studies comparing MVIV to surgery. Sixteen studies[17-31] were single arm studies with no comparator group (variously described by study authors as case series, prospective cohort studies, retrospective cohort studies). These studies made formal or informal comparisons before and after the intervention and described outcomes in the single arm following the procedure. Twelve single arm studies[17,18,23-32] investigated transcatheter mitral VIV implantation (MVIV), while four[19-22] investigated transcatheter tricuspid VIV implantation (TVIV) procedures.

Country of Origin

The eligible SR[14] was conducted in China. One retrospective cohort study[15] with a comparison group was conducted in the United States and the other[16] in Spain. Three[17,19,26] single arm studies were conducted in Brazil, one[23] in Australia, five[18,24,27,32] in the United States, one[31] in Japan, two[20,29] in Israel, two[21,30] in Italy, and one in Canada.[28] One single arm study[22] was conducted in Austria, Belgium, Canada, France, Germany, Italy, Portugal, Saudi Arabia, Switzerland United States, while another[25] was conducted in Canada, France, and United States.

Patient Population

The relevant patient population in the SR[14] was patients undergoing MVIV procedures for degenerated mitral bioprostheses. The characteristics of patients (n = 172) were not available for every study in the SR. Among studies that reported characteristics, the mean age of patients was 75 years and 47% were male. The mean Society of Thoracic Surgeons (STS) score was 16.8%. Approximately 38% of patients had pulmonary hypertension, 15% had coronary artery disease, 35% had chronic renal failure, 17% had diabetes, and 42% had atrial fibrillation. Around 97% were in New York Heart Association (NYHA) class III or higher, indicating functional impairment and symptoms that interfere with activities or daily life.

The patient population in one retrospective cohort study was patients with severely degenerated mitral valve prostheses.[15] There were 62 patients who received MVIV, with a mean age of 64 years. Approximately 39% were male, 76% had atrial fibrillation, 53% had coronary artery disease, 47% had a previous coronary artery bypass graft (CABG), 26% had previous aortic valve replacement surgery, 31% were in NYHA class IV, 71% were undergoing the procedure for stenosis, and the mean time from their previous procedure was 10 years. There were 59 patients who received surgical mitral valve replacement (SMVR), with a mean age of 75 years. Approximately 39% were male, 27% had atrial fibrillation, 30% had coronary artery disease, 25% had previous CABG, 7% had previous

aortic valve replacement surgery, 32% were in NYHA functional class IV, 49% were undergoing the procedure for stenosis, and the mean time from their previous procedure was 8.2 years.

In the other retrospective cohort study, the patient population was those undergoing reoperative mitral valve procedures for failed bioprostheses.[16] There were 21 patients who underwent MVIV, with a mean age of 77 years. Approximately 62% were female, 86% were in NYHA functional class III or IV, 43% had atrial fibrillation, 9.5% had vascular disease, 90% had severe pulmonary hypertension, and 14% had a patent bypass graft. There were 40 patients who underwent minimally invasive mitral valve replacement through a right anterior minithoracotomy (MIMVR), with a mean age of 67 years. Approximately 56% were female, 71% were in NYHA functional class III or IV, 10% had atrial fibrillation, 15% had vascular disease, 34% had severe pulmonary hypertension, and 17% had a patent bypass graft.

In 15 of 16 single arm studies, for both MVIV and TVIV, the patient population was those who were at high risk for repeat surgical valve replacement. This was based on explicit criteria such as the STS score or EuroSCORE, or based on frailty, co-morbidities, anatomical reasons, or the opinion of the care team. One of the single arm studies[18] which relied on registry data did not explicitly outline eligibility criteria for receiving a transcatheter procedure but noted that the patients included in the study had higher predicted surgical risk than patients in the registry who received repeat surgery. Another single arm study did not include explicit criteria or a detailed explanation around surgical risk (see Appendix 2 for characteristics of patients in this study).[22]

Patients in the 12 single arm studies[17,18,23-32] involving MVIV were generally older (mean age of patients ranged from 62 to 82 years) with co-morbidities and were in NYHA class III or IV (see Table 3 in Appendix 2 for details).

In studies involving TVIV,[19-22] patients were deemed to be at high surgical risk, commonly had co-morbidities and were generally in NYHA class III or IV at baseline. The mean age of patients in three TVIV studies[19,20,22] ranged from 33 to 63 years (one study[21] did not report a mean age; the age range in this study was 49 to 75 years). The study with a mean age of 33[19] involved younger patients with congenital diseases (e.g. Ebstein's anomaly), while in one TVIV study[22] with a mean age of 40, 56% of patients had congenital diseases. In the TVIV study[33] with an age range of 49 to 75 years, co-morbidities were common (80% had arrythmia, 60% had hypertension) and all patients were in NYHA class III or IV. Patients in the other TVIV study[20] had a mean age of 63 and 86% had a rheumatic tricuspid valve pathology. Co-morbidities were common in this study (86% had atrial fibrillation, 57% had severe pulmonary hypertension) and the mean EuroSCORE II was 13.6%. See Table 3 in Appendix 2 for full details.

Interventions and Comparators

In the eligible SR, the intervention of interest for this report was MVIV for degenerated mitral bioprostheses via transapical or transseptal access. Studies used Sapien XT, Sapien, Sapien 3, Melody, Tiara, Lotus, Tendyne, or Direct Flow valves (exact proportion not reported for MVIV specifically).[14] All included studies were single arm studies with no comparison group; pre- and post-intervention comparisons were reported for NYHA class.

In one retrospective cohort study, the intervention was a balloon-expandable transcatheter heart valve (seven patients with Sapien, 14 with Sapien XT, 41 with Sapien 3) implanted via transapical or transseptal access (transcatheter mitral valve-in-valve replacement).[15] The

comparator was surgical mitral valve replacement (SMVR) performed via standard sternotomy, thoracotomy, or minithoracotomy.

In the other retrospective cohort study, the intervention was transcatheter transapical mitral valve-in-valve implantation (18 patients with Sapien XT and 3 patients with Sapien 3).[16] The comparator was minimally invasive mitral valve replacement through a right anterior minithoracotomy (MIMVR).

The intervention in 12 of the single arm studies was a MVIV for degenerated mitral valve bioprostheses. The approaches (e.g. transapical, transseptal) and specific valves used varied across studies. In terms of valves, two studies[17,26] used Braile Inovare, three[27,29,30] used Sapien, one[31] used Sapien XT, two[18,23] used Sapien 3, one[32] used Melody, and three[24,25,28] studies used a mixture.

The intervention in four of the single arm studies was a TVIV procedure for degenerated tricuspid valve bioprostheses. These studies also varied in terms of valves and access. One study[19] used Braile Inovare valves, one[21] used Sapien 3, and two[20,22] used a mixture.

Outcomes

The eligible SR[14] reported the following in-hospital hospital outcomes: success rate, mortality, bleeding, stroke, myocardial infarction (MI), new arrythmia, and acute kidney injury. The authors also made a formal statistical comparison of the proportion of patients with NYHA $\geq$ III before and after the procedure using a chi-square test. Data was not available from all eligible studies for NYHA, and for outcomes at 30 days and 6 months (see Table 6 in Appendix 4).

One retrospective cohort study measured in-hospital death, vascular complications, bleeding complications, stroke, arrythmia, left ventricular outflow tract (LVOT) obstruction, prolonged ventilation (>24 hours), as well as 30-day and 1-year mortality.[15] The authors also reported the mean time spent in the intensive care unit (ICU) and mean length of stay after the procedure. Differences in continuous outcomes were compared using a 2-sample t test or Wilcoxon rank sum test. Differences in the proportion of patients experiencing outcomes were analyzed using the chi-square test or Fischer exact test, and for survival data, the log-rank test.

The other retrospective cohort study measured in-hospital death, reoperation for bleeding, low cardiac output syndrome and pulmonary complications, and reported the adjusted odds ratio (and 95% confidence intervals [CI] for these outcomes).[16] The authors also measured the mean length of ICU stay and length of hospital stay but did not make a statistical comparison between groups for these outcomes. They evaluated survival at 2 years and compared the rates between the two groups using a log-rank test.

Single arm studies of MVIV and TVIV all reported the proportion of patients in particular NYHA classes before and after the procedure, or the mean NYHA class before and after the procedure. These measures could be compared. One MVIV study[32] made a formal statistical comparison of the mean NYHA class preimplant versus postimplant using a paired t test. One of the TVIV studies[22] measured the proportion of patients with NYHA class I or II at 30 days and at last follow-up (median of 13 months post-procedure) and compared this proportion to baseline using McNemar's test. The other studies did not make formal statistical comparisons of NYHA class before and after the procedure.

Single arm studies also reported descriptive statistics of various measures at different timepoints following the procedure (e.g. in-hospital, 30 day, and at long-term follow-up). The specific outcomes varied across studies, but included: success rate, mortality, MI, stroke, major vascular complications, bleeding, acute kidney injury, and readmission. See Table 3 in Appendix 2 for specific outcomes and timepoints measured in each study.

Summary of Critical Appraisal

There were several methodological concerns for the eligible SR.[14] The authors did not clearly report PICO elements or give any details around whether methods were established prior to conduct of the review. Extraction was performed in duplicate, but it was unclear whether study selection was also done in duplicate. The details of included studies were not described in detail and there was no risk of bias assessment performed. It was unclear whether the method of combining NYHA data for the pre- and post-intervention comparison was appropriate and sources of heterogeneity between studies were not described. All studies included in this SR were single arm studies, and the overall number of patients included was 172 (the before-after comparison of NYHA class included 57 patients pre-procedure and 39 patients after).

Both retrospective cohort studies[15,16] clearly described the study aim and provided clear descriptions of the study population and intervention of interest. The findings of both studies were generally well described, though one study[15] did not provide measures of variability around between-group differences.

A central limitation in the one of the retrospective studies was the presence of baseline imbalances between the two groups.[15] The analysis did not incorporate any methods to handle these baseline imbalances, and thus there was potential for bias due to confounding. However, the group receiving the transcatheter group was older and generally had higher rates of comorbidities, which would have biased the results in favour of the surgical group. The authors noted that participants would have been selected into a group based on their characteristics and the likelihood of success of a particular procedure, which also created concerns surrounding selection bias. Another concern in this study was that participants in the two groups were recruited over different time periods, since the transcatheter procedure was only available for the later part of the study period. Differences in management and co-interventions over time may therefore introduce additional bias. The authors noted that there were no major innovations over this period; however, no further explanation or justification was reported.

In the other retrospective cohort study, there were also baseline imbalances between study groups.[16] The authors in this study used propensity scores in an attempt to adjust for potential confounding these imbalances may have introduced. The authors included age, sex, and various diagnostic factors and co-morbidities in their model. However, given the extent of the differences between the two groups at baseline, it is possible that there were other important confounders which were not captured in the model. Therefore, there was still potential for residual confounding, which in turn raised concerns around the validity of the estimates reported. One consideration is that in this study, the transcatheter group was also older and had more co-morbidities than the surgery group, suggesting any bias may have favoured the surgery group. Selection bias was also a concern in this study as treatment was based on patient characteristics and suitability for a particular intervention.

Both retrospective cohort studies had small sample sizes (n = 121 and n = 61) and low event rates (e.g. 1 in-hospital death and 1 stroke in the MVIV group one study[16]), and

neither provided any information about statistical power. Thus, it was unclear whether these studies had sufficient power to detect meaningful differences between groups. One retrospective cohort study[15] did not provide any measures of precision around between-group differences, making it difficult to judge the extent of concern in this study. In the other retrospective cohort study, there was wide variability around the effect estimates (wide 95% CIs), raising concerns around imprecision.[16]

The generalizability of the results in these studies was unclear. One retrospective cohort study[15] recruited patients from three centers in the US; however, it was unclear whether patients who attended these centers reflected the typical population of patients undergoing such procedures. In this study, complex patients (those requiring CABG or double valve replacement) were excluded, suggesting their results may not be applicable to more complex patients. The other retrospective cohort study[16] was conducted at a single center in Spain and the authors noted that the study encompassed the "initial learning curve" with MVIV. Thus, the extent to which the study results apply in the current routine care context, was unclear.

The major limitation of all the eligible single arm studies is lack of a comparison group. Lack of a comparison group makes it impossible to draw conclusions about the relative efficacy and safety of transcatheter VIV procedures compared to surgery or medical management. While studies did report NYHA at baseline and follow-up, permitting comparison of functional status before and after the procedure, only two studies made a formal statistical comparison of NYHA before and after. For other outcomes such as mortality, stroke, and bleeding, it was not possible to compare transcatheter VIV approaches to other treatment approaches. Another concern with single arm studies is that they were generally small (11 out of 12 MVIV studies had sample sizes ≤ 60 and three out of four TVIV studies had sample sizes ≤7), and conducted at one (or a few) centers, making it unclear whether included patients are representative of typical patients undergoing such procedures. One study[18] included all patients (n = 1529) undergoing MVIV in a voluntary registry at 295 sites between from 2015 to 2019, and may offer greater generalizability. Further, 11 of 16 single arm studies reported on consecutive patients at their center (or total number of patients in a registry), suggesting that the subjects reported on were representative of all patients receiving transcatheter VIV procedures at their center(s). Single arm studies were generally well-reported, and clearly described their aims, outcomes, and findings.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness of Mitral Valve-in-Valve Approaches

Success rate

The eligible SR[14] reported that the technical success of MVIV procedures was 97% (167/172). Among the ten single arm studies reporting this outcome, success rate ranged from 86 to 100%. Success rates in individual studies were 86% (6/7),[23] 97% (1480/1529),[18] 97% (58/60),[25] 98% (49/50),[17] 99% (72/73),[28] 100% (15/15),[24] 100% (19/19),[27] 100% (12/12),[26] and 100% (9/9).[29]

Mortality

Two studies reporting on in-hospital mortality included comparator groups. In one study, there was no significant difference between surgery and MVIV for the outcome of in-hospital death (3.4% for surgery versus 3.2% for MVIV, P=1.00).[15] The other study reported crude event rates, as well as adjusted odds ratios (aOR).[16] The rate of in-hospital deaths was not significantly different between groups (7.5% in the surgery group compared to 4.7% in the MVIV group; aOR 2.46, 95% CI 0.16 to 36.7).

The eligible SR[14] reported an in-hospital mortality rate of 5.2% (9/172) for patients receiving MVIV procedures. Seven single arm studies reported short-term mortality (described variously as intraoperative, operative, procedural, or in-hospital) in patients who received MVIV procedures. In these studies, the short-term mortality ranged from 0% to 4%. Short-term mortality in individual studies was 0% (0/15),[24] 0% (0/13),[32] 0% (0/12),[26] 0% (0/9),[29] 2% (1/50),[17] 3% (2/60),[25] and 4% (61/1529).[18]

One non-randomized study that included a comparison group reported 30-day mortality. There was no significant difference between groups for 30-day mortality (3.4% for surgery versus 3.2% for MVIV, P=1.00).[15] The eligible SR[14] reported a 30-day mortality of 7.5% (11/147). Nine single arm studies reported 30-day mortality, which ranged from 0% to 15%. Mortality at 30 days in individual studies was: 0% (0/15),[24] 0% (0/19),[27] 0% (0/31),[28] 5% (3/60),[25] 5% (calculated from Kaplan-Meier curve),[18] 9% (2/22),[30] 12% (6/50),[17] 14% (1/7),[23] and 15% (2/13).[27]

One non-randomized study[15] that included a comparison group reported 1-year mortality. There was no significant difference in 1 year-mortality between surgery and MVIV (11.9% for surgery versus 11.3% for MVIV, P=0.92). The other non-randomized study with a comparator group found no difference in the proportion of patients surviving to 2-years between surgery and transcatheter MVIV (87.1% for surgery versus 86.1% for MVIV [log-rank P=0.148]).[16]

The eligible SR of single arm studies reported a 6-month mortality rate of 18.8% (16/85) among patients receiving MVIV procedures.[14] Four single arm studies reported mortality at 1-year, which was 14%[25] (from Kaplan-Meier curve), 17%[18] (calculated from Kaplan-Meier curve), 25%[32] (from Kaplan-Meier curve), and 27%[24] (4/15). One single arm study reported survival at 3 years to be 91% (among patients who could be followed up).[30] Four single arm studies reported mortality at last follow-up. In one study, the follow-up ranged from 207 to 513 days and the authors reported there had been no deaths.[31] Another study reported a mortality rate of 46% at a median follow-up time of 4 years.[32] One study reported a mortality rate of 5% at a mean follow-up of 339 days,[27] and another reported a mortality rate of 8% with a median follow-up of 612 days.[26]

Myocardial infarction

The eligible SR reported no MIs in-hospital, at 30 days, or at 6 months.[14] Two single arm studies reported short-term (described as periprocedural or “after the procedure”) rates of MI, which were 0.3% (5/1529)[18] and 0%(0/60).[25] The rate of MI at 30 days was reported in five single arm studies, and was 0% (0/15),[24] 0% (0/19),[27] 0% (0/31),[28] 4% (2/50),[12] and 4.5% (1/22).[30] The rate of MI at >30 days was reported as 0% (0/31) in one study.[28]

Stroke

In one non-randomized study that included a comparator, the rate of major stroke was numerically lower in the MVIV group compared to the surgery group (3.4% for surgery

versus 0% in MVIV group, P=0.24), but this difference was not statistically significant.[15] In the other non-randomized study with a comparator, stroke occurred in 12.5% of the surgery group and 4.7% of the MVIV group (aOR 0.89, 95% CI 0.48 to 16.2).[16]

In the eligible SR, the stroke rate was 1.7% (3/172) in hospital, 3.2% (3/95) at 30 days, and 5.4% (3/56) at 6 months.[14] Four single arm studies reported short-term (periprocedural, "after the procedure", procedural, or early stroke) rates, which were 0% (0/9),[29] 0% (0/19),[27] 0.7% (10/1529),[18] and 8% (1/12).[26] Seven single arm studies reported stroke rates at 30 days, which were 0% (0/15),[24] 0% (0/7),[23] 0% (0/22),[30] 0% (0/19),[27] 1% (from Kaplan-Meier curve),[18] 1% (1/31),[28] and 2% (1/50).[17] Stroke rate at >30 days was reported in one study, and was 1% (1/31).[28]

Bleeding

In one non-randomized study with a comparator group, the rate of life-threatening bleeding (11.9% for surgery versus 6.5% for MVIV, P=0.30) was numerically lower in the transcatheter MVIV group, but the difference was not statistically significant.[15] In the other non-randomized study with a comparator group, the rate of reoperation for bleeding was 14.6% in the surgery group versus 4.7% in the MVIV group (aOR 0.43, 95% CI 0.50 to 3.67), a finding which was not statistically significantly different.[16]

The eligible SR reported an in-hospital bleeding rate of 8.7% (15/172) for patients receiving MVIV.[14] One single arm study[32] reported that 7.7% (1/13) of patients experienced retroperitoneal bleeding requiring surgery, while another single arm study[25] reported a major procedural bleeding rate of 7% (4/60). One study reported that 11% (1/9) of patients experienced early major bleeding.[29] The rate of bleeding at 30 days was 4% (2/50) in one study[17] and 14% (1/7) in another study.[23] One single arm study reported a major bleeding rate of 8.2%[28] (6/31) at 30 days, and the same study[28] reported a major bleeding rate of 0% (0/31) >30 days after the procedure.

NYHA

The eligible SR[14] compared the proportion of patients with NYHA $\geq$ III (%) at baseline to the proportion after the procedure. The proportion was 100% (57/57) before the procedure and 4% (1/39) after the procedure, a difference which was statistically significant (P<0.001).

All 12 single arm studies involving MVIV reported on the proportion of patients in different NYHA classes (or mean NYHA) at baseline and at various points post-procedure. These measures could then be compared. One study[32] made a formal statistical comparison, reporting that the mean NYHA class "preimplant" was 3.5 (SD 0.5) and 1.9 (SD 0.9) "postimplant" (P for difference <0.01). These authors also reported a mean NYHA class at 1 year (1.9 [SD 0.8]), 3 years (1.8 [SD 1.0]), and 5 years (2.0 [SD 0.8]) of follow-up but did not formally compare this to baseline.

The other single arm studies did not make a statistical comparison of NYHA class before and after the procedure. In all studies, the majority of patients were in NYHA class III or IV at baseline. All studies reported higher proportions of patients in NYHA class I or II after the procedure (at 30 days, 1 year, and long-term follow-up) compared to baseline. See Appendix 4 for details of individual studies.

Other complications

In one non-randomized study[15] with a comparison group, patients in the MVIV group had statistically significantly lower rates of new atrial fibrillation compared to the surgery group

(30.5% for surgery versus 1.6% for MVIV, P<0.001) and prolonged ventilation for >24 hours (33.9% for surgery versus 4.8% for MVIV, P<0.001). The rate of vascular complications (5.1% for surgery versus 1.6% for MVIV, P=0.36) was numerically lower in the MVIV group compared to the surgery group, but this was not statistically significant.

In the other non-randomized study[16] with a comparison group, pulmonary complications occurred in 20% of the surgery group and 9.4% of the MVIV group (aOR 1.13, 95% CI 0.16 to 7.81), which was not statistically significantly different.

The eligible SR[14] reported that the in-hospital rate of new arrhythmia was 1.7% (3/172) and the in-hospital rate of acute kidney injury was 4% (7/172) in patients receiving MVIV procedures.

Acute kidney injury and other renal outcomes were reported in seven of the single arm studies. One study reported a procedural acute kidney injury rate of 0% (0/12).[26] Another study reported an acute kidney injury rate during hospitalization of 8% (1/13).[32] The rates of acute kidney injury at 30 days were 5% (1/22),[30] 7% (1/15),[24] and 14% (1/7).[23] The rate of acute renal failure at 30 days was 30% (15/50) in one study,[17] and the rate of acute renal failure requiring dialysis was 1% (1/31) in another study.[28] One study reported that 2% of patients newly required dialysis at 30 days.[18] Full details of other complications are in Appendix 4.

Author conclusions

Authors of one non-randomized study[15] with a comparison group concluded that there appeared to be no difference in mortality between groups at 30 days and 1 year, which suggested that MVIV was an effective alternative to surgery for selected patients with failed bioprosthetic mitral valves. However, the authors also noted that their findings need to be confirmed by long-term studies with larger sample sizes.

Authors of the other non-randomized study[16] with a comparison group concluded that MVIV was safe and effective and that there was a trend towards better outcomes for MVIV compared to surgery. They also suggested that MVIV represented an option for select patients with malfunctioning mitral bioprostheses.

The eligible SR of single arm studies[14] concluded that MVIV for degenerated mitral bioprostheses was highly feasible and safe in those who were not candidates for surgery, though they highlighted the lack of comparison to surgical valve replacement and the need for more long-term data.

Authors of the single arm studies included in this report generally concluded that MVIV procedures were feasible, safe, and effective for patients with degenerated bioprostheses at high surgical risk. Study authors also highlighted improvements in symptoms and function following the procedure compared to baseline, suggesting MVIV led to symptomatic and functional improvement. One study also highlighted the importance of access, noting that transseptal access may be associated with lower mortality compared to transapical access.[18]

Clinical Effectiveness of Tricuspid Valve-in-Valve Approaches

Success rate

Success rate was 99% (150/152),[22] 100% (5/5),[21] and 100% (7/7)[19] in the three single arm studies reporting it.

Mortality

Mortality was reported at 30 days in two single arm studies and was 0%[21] (0/5) and 3%[22] (5/152). Three single arm studies reported mortality at long-term follow up. One study[19] reported no deaths in any patients with a mean of 1.2 years follow-up. Another reported a mortality rate of 14% (1/7) at a mean of 8 months of follow-up.[20] Finally, one study reported a mortality rate of 11% (17/152) at a median of 13 months of follow-up.[22]

Myocardial infarction

One single arm study reported no MIs (0/5) at 30 days.[21]

Stroke

One single arm study reported no strokes (0/5) at 30 days.[21] Another single arm study reported a stroke in 14% (1/7) of patients over a mean follow-up of 8 months.[20]

Bleeding

One single arm study reported no bleeds (0/5) at 30 days.[21]

NYHA

Four single arm studies[19-22] measured NYHA class at baseline and at different points after the procedure, allowing for comparison before and after. One study[22] made a statistical comparison and reported that the proportion of patients in NYHA class I or II was statistically significantly higher at both 30 days (87% versus 28% at baseline, p<0.001) and at last follow-up (85% versus 28% at baseline, P<0.001), compared to baseline. From this, the authors concluded that most patients had an improvement in functional status following the procedure. In the other single arm studies, the proportion of patients in NYHA class I or II post-procedure also increased compared to baseline (see Appendix 4) but there was no statistical comparison.

Other complications

The rate of postoperative acute kidney injury not requiring dialysis was 29% (2/7) in one single arm study,[19] while the rate of acute kidney injury at 30 days was 20% (1/5) in another study.[21]

Author conclusions

Authors of single arm studies involving TVIV procedures concluded that the procedure was feasible, safe, and effective in patients at high risk for surgery, but acknowledged the need for long term data and higher quality studies. Authors also concluded that the procedure was associated with improvement in symptoms and/or function.

Cost-Effectiveness of Mitral or Tricuspid Valve-in-Valve Approaches

No relevant evidence regarding the cost-effectiveness of transcatheter aortic valve implantation for degenerated mitral or tricuspid bioprostheses was identified; therefore, no summary can be provided.

Limitations

There was a lack of high-quality studies examining the clinical effectiveness of transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses, and no relevant economic evaluations. Available clinical evidence was comprised mainly of small,

single arm studies or case series. The one eligible SR[14] included only single arm studies, with a relatively low total number of patients (n=172, with fewer patients for some outcomes), and had serious methodological concerns due to unclear reporting and analysis techniques. While single arm studies provide some insight on various clinical outcomes, the lack of a comparison group makes it impossible to evaluate the relative efficacy and safety of transcatheter approaches compared to surgical approaches. There were few studies available on use of TVIV in particular, which may reflect the fact that tricuspid valve replacements are uncommon surgeries.[34]

Two of 19 studies[15,16] included in this report (both reporting on MVIV) contained comparison groups (surgery), and both were small (n=121, n=61) non-randomized studies, with serious methodological concerns, particularly the potential for bias due to confounding. A major challenge with these studies was that patients tended to be assigned to a treatment based on what was deemed to be the best option for them (e.g., based on specific characteristics, those who received transcatheter approaches were not candidates for surgery). This created inherent concerns with selection bias and bias due to confounding (particularly confounding by indication) in these studies. While the issue of selecting patients for a particular procedure may be understandable given the clinical context of the problem, it makes comparison between transcatheter and surgical approaches challenging, thus making it difficult to draw firm conclusions regarding the comparative effectiveness of transcatheter and surgical replacement. Another consideration was that the patients who received the surgical intervention in one of the non-randomized studies with a comparison group all received minimally invasive surgery with minithoracotomy.[16] Therefore, the results from this study may only be relevant in contexts where the surgical option for this procedure involves minithoracotomy. An additional challenge is that studies in this review used different access routes for transcatheter procedures (e.g. transseptal, transapical, a mixture), which may make it difficult to directly compare the results of individual studies, particularly because transseptal access may confer reduced mortality compared to transapical access.[18] Further, the results of studies involving one type of access may not be generalizable to centers or institutions where another type of access is used.

Overall, the lack of high-quality evidence makes it difficult to draw conclusions about the effectiveness of transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses.

The generalizability of the evidence to the Canadian context was difficult to establish. For mitral valves, one Canadian study[28] was available; however, this study reported outcomes for 31 patients between 2007 and 2013 at a single center. For tricuspid valves, Canadian data were included in the registry of one study;[22] however, there was no description of how many Canadian cases were included and the relevance of this study to the Canadian context was also unclear.

Conclusions and Implications for Decision or Policy Making

This report identified one SR of single arm studies, two non-randomized studies with comparison groups, and 16 single arm studies on transcatheter aortic valve implantation for patients with degenerated mitral or tricuspid bioprostheses. The eligible SR, two comparative non-randomized studies, and 12 single arm studies examined mitral valves, and four single arm studies examined tricuspid valves. There was no evidence regarding the cost-effectiveness of transcatheter aortic valve implantation for patients with degenerated mitral or tricuspid bioprostheses.

In patients with degenerated mitral valve bioprostheses, one study[15] that included a comparison group concluded that there was no difference in mortality between a transcatheter approach and surgical replacement, while authors of the other study involving a comparison group[16] concluded that a transcatheter approach was safe and effective compared to surgical replacement. These authors also reported a trend towards improved clinical outcomes (such as stroke, pulmonary complications, and bleeding) with the transcatheter procedure though estimates were imprecise with wide 95% CIs.[16] In both studies, there was no statistical difference between transcatheter and surgical procedures in the rate of in-hospital death, and no difference in mortality at 30 days, 1 year, or 2 years.[15,16] The authors of both studies suggested that transcatheter aortic valves were an option for select patients with failed bioprosthetic mitral valves. In the SR of single arm studies, and 12 single arm studies involving MVIV, authors concluded that based on low mortality rates and low rates of complications, MVIV procedures appeared feasible, effective, and safe, in patients at high risk for surgery. Mitral VIV procedures also generally improved NYHA class, leading authors to conclude that these procedures improved symptoms and function.

In patients with degenerated tricuspid valves at high risk for surgery, authors also concluded that based on low mortality rates and low complication rates, that TVIV procedures were feasible, effective, and safe. Studies involving TVIV also demonstrated improvements in patient NYHA class compared to baseline, leading authors to conclude that transcatheter valves resulted in improved functional status in most patients.

As highlighted above, there were major methodological concerns with all eligible studies. In particular, there were concerns around selection bias and bias due to confounding in the retrospective cohort studies that included comparison groups, and concerns around lack of a comparison group in the single arm studies. Due to these concerns, there was low certainty in all results. Existing reviews have also highlighted limitations of the data around transcatheter procedures for degenerated mitral or tricuspid bioprostheses, similarly noting small sample sizes, lack of control groups, and poor quality studies.[4,8]

As outlined in Appendix 5, there are several additional studies of interest, comprised mainly of case series. While these studies did not provide information relevant to the current report since they did not include comparisons to surgical replacement or permit comparison of outcomes from baseline to follow-up after transcatheter aortic valve implantation, they may provide additional insight on this topic.

Given the limitations and methodological concerns with available evidence, it was difficult to draw conclusions regarding the clinical effectiveness of transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses relative to surgical replacement or medical management. Existing evidence provided limited insight for decision and policy making. As noted in a recent review,[4] research on transcatheter procedures for degenerated mitral and tricuspid bioprostheses is considered to be at an early stage, with much of the available research coming in the form of case series or uncontrolled single arm studies. This review also highlights that while there is limited evidence on transcatheter approaches, there also remains limited evidence on the effectiveness of surgical approaches. Based on the current body of evidence, it appears that further investigation is warranted in this area.

Future studies may be helpful in investigating the clinical effectiveness of transcatheter aortic valve implantation for patients with degenerated mitral or tricuspid bioprostheses. These studies should include larger sample sizes and incorporate methods to address selection bias as well as robust and well-described methods to address bias due to

confounding (whether by design or using statistical techniques if possible). It is acknowledged that this may be challenging, since confounding by indication is likely to be a concern in such studies (i.e., patients are generally specifically selected to receive transcatheter approaches due to high surgical risk). Randomized trials may even be impossible since many patients will be at prohibitive risk of surgery, therefore precluding them from being randomized to this arm. The role of access route may also warrant further investigation in transcatheter procedures, as transseptal access has been associated with a lower mortality compared to transapical access.[18] Finally, future studies should also investigate the cost-effectiveness of transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses, as there was no evidence on this topic that was identified for inclusion in this report. Existing reviews have also outlined the need for well-designed studies and future research in this area, further suggesting there is a need to identify appropriate selection of patients for transcatheter procedures versus surgical procedures to inform clinical decision-making.[4,8]

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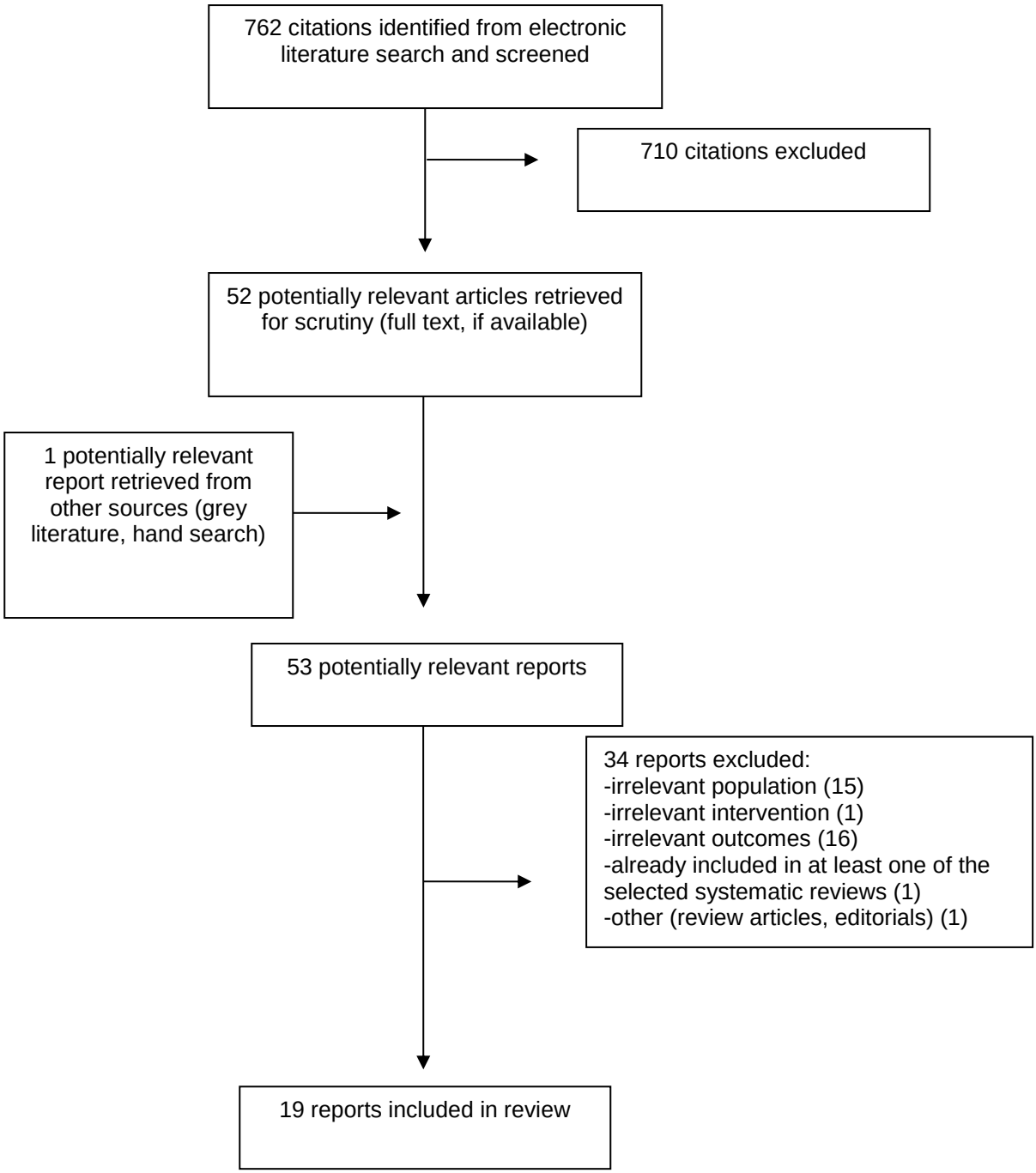
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Objective, study designs and numbers of primary studies included, databases, search date	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Hu et al. 2018[14] China Funded by National Natural Science Foundation of China	**Objective** Review the outcomes of TMVIV implantation for degenerated mitral bioprostheses and TMVIR implantation for failed annuloplasty rings **Studies** 101 studies in total; 66 studies described TMVIV for degenerated bioprostheses; study design of eligible studies not described (authors did not appear to exclude any study designs; all included studies were single arm studies with no comparator group) **Databases** PubMed and Web of Science **Search date** 2000 (day and month not specified) to March 30, 2018	**172 patients** undergoing TMVIV implantation for degenerated mitral bioprostheses Characteristics were not available in every study Mean age 75 (reported in 119 patients) 47% male (reported in 114 patients) Mean Logistic EuroSCORE 36.4% (reported in 69 patients) and mean STS score 16.8% (reported in 86 patients) 38% had pulmonary hypertension, 15% CAD, 35% chronic renal failure, 17% diabetes, 42% atrial fibrillation (reported in 122 patients) 52% had a history of heart surgery (reported in 122 patients 97% had NYHA class III or higher (reported in 111 patients) Mitral valve failure mode was regurgitation in 49%, stenosis in 32%, and mixed in 19% (reported in 144 patients) Mean LVEF 51.2% (reported in 73 patients)	**Intervention** TMVIV implantation for degenerated mitral bioprostheses **Comparator** None (NYHA class could be compared to baseline)	**In-hospital outcomes** Success rate, mortality, bleeding, stroke, MI, new arrythmia, acute kidney injury, NYHA class **30 day and 6 month outcomes** Death, stroke, MI, thrombus, pseudoaneurysm, device failure, device migration

CAD = coronary artery disease; LVEF = Left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; TMVIR = transcatheter mitral valve-in-ring; TMVIV = transcatheter mitral valve-in-valve.

Table 3: Characteristics of Included Non-Randomized Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Mitral valve-in-valve procedures				
da Costa et al. 2020[17] Brazil Half of the valves used in the study were donated by Braile Biomedica and remaining valves were purchased at a subsidized cost	Case series (prospective single centre database analysis)	**50 patients** undergoing MVIV between May 2015 and July 2018 at a single center **Patients were selected for transcatheter approach based on risk assessment** (STS ≥ 8 or EuroSCORE II ≥ 8.0, presence of comorbidities, number of previous surgeries, frailty, and general clinical conditions) **Exclusion criteria** Active endocarditis, pregnancy, presence of prosthetic valve thrombosis or thrombus in left ventricle, paravalvular regurgitation Mean age 65 28% male 14% had diabetes, 44% systemic arterial hypertension, 30% dyslipidemia, 6% COPD, 56% chronic renal failure (Crcl < 60 mL/min), 18% CAD, 10% prior CABG, 72% permanent atrial fibrillation, 20% NHYA class II, 58% NYHA class III, 22% NYHA class IV Mean time since last valvular surgery 12 years Mean STS score (%) 8.3 Mean EuroSCORE II (%) 12.4	**Intervention** MVIV through left anterolateral minithoracotomy for transapical access; valve was Braile Inovare **Comparator** None (NYHA class could be compared to baseline)	Success rate **30 day postoperative data** MI, stroke, major vascular complications, major bleeding, acute renal failure, sepsis, mortality, NYHA
Keenan et al. 2020[23] Australia No financial support	Case series	**7 patients** undergoing MVIV procedures between December 2017 and November 2018 at a single center Patients had structural deterioration of mitral bioprosthetic valves and were considered **high risk for redo valve surgery** or were young	**Intervention** Transseptal MVIV procedure using Edwards Sapien 3 valve **Comparator** None (NYHA class could be compared to baseline)	Success rate **30 day outcomes** Mortality, stroke, bleeding, transfusion, major vascular complications, readmission, NYHA class

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		patients likely requiring multiple reoperations 3 patients were young Indigenous Australians (age range 33 to 41) with rheumatic heart disease who were not suitable for mechanical prostheses 4 patients were older persons (age 82 to 92) who were high risk for reoperative surgery Overall sample Mean age 82 43% male 71% had hypertension, 14% diabetes, 14% COPD, 43% atrial fibrillation, 14% previous stroke, 43% previous CABG 29% NYHA class II, 29% NYHA class III, 43% NYHA class IV Median EuroSCORE II 7.3 Median STS score 4.3 Median time since last MVR 11 years		
Okoh et al. 2020[24] United States Funding not described	Case series	**15 patients** who underwent MVIV due to degenerative biological valve prosthesis between July 2013 and September 2016; **considered high risk for reoperative surgical MVR** Mean age 69 years 87% female 40% Caucasian, 40% African American, 20% Hispanic 80% had NYHA class III or IV Mean STS score 9.6	**Intervention** MVIV for failed bioprosthetic mitral valves (12 cases via transapical approach, 2 through median sternotomy, 1 via transseptal approach) Sapien XT in 10 patients, Sapien in 4 patients, and Sapien S3 in 1 patient **Comparator** None (NYHA class could be compared to baseline)	**Procedural** Success rate, acute kidney injury, MI, disabling stroke, new onset atrial fibrillation **30 day outcomes** Mortality, disabling stroke, rehospitalization, NYHA class **1 year outcomes** Mortality, NYHA class

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		73% had pulmonary hypertension, 53% CAD, 40% chronic lung disease, 47% chronic atrial fibrillation, 47% systolic heart failure		
Whisenant et al. 2020[18] United States Funding not reported (all statistical analyses were performed by Edwards Lifesciences, manufacturer of the valve)	Registry-based prospective cohort study (no comparator)	**1529 patients** undergoing MVIV at 295 sites in the United States between June 2015 and July 2019; no explicit criteria outlined; however, **authors note that patients in study were older and had higher predicted operative risk than those undergoing reoperation in the same database** (registry) Mean age 73 59% women 1.3% NYHA class I, 12% class II, 56% class III, 31% class IV 71% had atrial fibrillation, 17% stroke, 46% COPD, 35% previous CABG, 24% prior aortic valve procedure Mean STS score 11 (56% had score >8)	**Intervention** MVIV for degenerated bioprosthetic mitral valves using Edwards Sapien 3 valve (87% transseptal, 13% transapical) **Comparator** None (NYHA class could be compared to baseline)	**Primary outcome** 1-year mortality, procedural technical success **Secondary outcomes** 30-day mortality, procedural complications, in-hospital cardiovascular mortality, in-hospital all-cause mortality, NYHA class, mitral valve performance, quality of life
Yamashita et al. 2020[31] Japan Funding not reported; devices were supplied by Edwards Lifesciences	Prospective, non-comparative, non-randomized, interventional cohort study	**4 patients** with significant deterioration of an implanted bioprosthetic valve with stenosis, regurgitation, or both; heart failure with resistance to medications; **high operative risk** or contraindication to repeat replacement surgery (based on consensus of institutional heart team) at one institution between May 2017 to March 2020 Patient characteristics not described statistically Age range 69 to 85 75% female STS score range 8.4 to 11.8	**Intervention** MVIV procedure with Sapien XT valve via transapical approach **Comparator** None (NYHA class could be compared to baseline)	NYHA class at 7 days compared to baseline, median distance on 6-minute walk test at 7 days and 30 days compared to baseline Adverse events within 30 days Symptoms at last follow-up

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		25% had hypertension, 25% diabetes, 25% dyslipidemia, 100% chronic lung disease, 25% prior cerebrovascular event, 50% chronic atrial fibrillation, 75% two or more prior cardiac surgeries, 25% previous CABG		
Joseph et al. 2019[32] United States Funding not reported	Retrospective cohort (no comparator)	**13 patients** who underwent percutaneous MVIV between July 2011 to October 2013 Patients had significant mitral prosthetic dysfunction and comorbidities **precluding repeat valve surgery** with sternotomy Mean age 75 54% female Mean STS mortality score (%) 13.5 Mean 8 years since last valve replacement Mean 1.4 previous sternotomies	**Intervention** MVIV procedure with Melody valve (transseptal puncture and apical rail) **Comparator** None (NYHA class could be compared to baseline)	Procedural death, 30-day mortality, 1 year mortality Mortality to last follow-up (median 4.4 years) Formal statistical comparison of mean NYHA class postimplant compared to preimplant, and reported mean NYHA class at 1-, 3-, 5-years
Elmously et al. 2018[27] United States Funded internally by New York Presbyterian-Weill Cornell Medicine	Retrospective review	**19 patients** undergoing transapical MVIV implantation between December 2013 and May 2017 at one center **Patients were considered high risk for redo surgical valve replacement** Mean age 78 64% female 47% previous CABG, 26% diabetes, 32% peripheral vascular disease, 32% COPD, 32% CKD, 47% atrial fibrillation Mean STS score 22 100% NYHA class III or IV 63% where MVIV performed as rescue procedure for patients	**Intervention** Transapical MVIV using Edwards Sapien **Comparator** None (NYHA class could be compared to baseline)	Success rate **30 days** Mortality, stroke, MI, blood transfusion **Last follow-up (mean 339 days)** Mortality, stroke, MI, NYHA class

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		with cardiogenic shock on inotropic or circulatory support		
Kamioka et al. 2018[15] United States Funding not reported	Retrospective cohort	**121 patients** with severely degenerated mitral valve bioprostheses between 2007 and 2017 (TMVR procedure started in 2012) **Exclusion criteria** Active endocarditis, required concomitant procedure for CAD or aortic disease, underwent additional valve replacement **TMVR** n=62 patients Mean age 75, 39% male, 76% with atrial fibrillation, 53% with CAD, 47% with previous CABG, 26% with previous aortic valve replacement, 27% with pacing device, 31% NYHA class IV; procedure reasons were stenosis (71%), regurgitation (50%), paravalvular leakage (8%); mean mitral valve gradient 12.1 mmHg, mean LVEF 55%, mean time from previous procedure 10.3 years **SMVR** n=59 patients Mean age 64, 39% male, 27% with atrial fibrillation, 31% with CAD, 25% with previous CABG, 7% with previous aortic valve replacement, 12% with pacing device, 32% NYHA class IV; procedure reasons were stenosis (49%), regurgitation (56%), paravalvular leakage (9%); mean mitral valve gradient 13.9 mmHg, mean LVEF 56%; mean time from previous procedure 8.2 years	**Intervention = TMVR** Transcatheter mitral valve-in-valve replacement; balloon-expandable transcatheter heart valve implanted from transapical or transseptal access; Sapien in 7 patients, Sapien XT in 14 patients and Sapien 3 in 41 patients **Comparator = SMVR** Surgical mitral valve replacement performed via standard sternotomy, thoracotomy, or mini-thoracotomy	In-hospital death, vascular complications, bleeding complications, stroke, arrythmia, LVOT obstruction, prolonged ventilation 30-day mortality, 1-year mortality
Eleid et al. 2017[25] Canada, France, United States Funding not reported	Case series	**60 patients** with degenerated mitral bioprostheses who underwent transcatheter transseptal MVIV procedure from January 2014 to March 2017	**Intervention** MVIV procedure with Sapien, Sapien XT, Sapien 3 valves via transseptal approach **Comparator**	Device success **Procedural outcomes** Conversion to open heart surgery, MI, stroke, emergency surgery, major

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Patients had **comorbid conditions that would preclude repeat sternotomy and valve replacement** **Exclusion criteria** Active endocarditis, prosthetic valve thrombosis Mean age 75 57% female 100% previous cardiac surgery 35% chronic lung disease, 8% previous stroke, 22% diabetes, 85% hypertension, 17% peripheral artery disease, 68% atrial fibrillation Mean STS score 12.5 45% NYHA class III, 55% class IV	None (NYHA class could be compared to baseline)	bleeding, vascular complications **30 days** Mortality, NYHA class **1 year** Mortality, NYHA class
Gaia et al. 2017[26] Brazil Funding not reported	Case series	**12 patients** with mitral prosthesis failure undergoing MVIV at one center between June 2010 to January 2013 **Inclusion criteria** Dysfunctional bioprosthesis in mitral position, STS >8% or logistic EuroSCORE >10, or clinical heart term judgement of **high surgical risk** **Exclusion criteria** Left atrial thrombus, presence of periprosthetic leak, prosthesis label size <25 or >31, presence of contraindications for anticoagulation Mean age 62 92% female 33% had COPD, 42% diabetes, 67% atrial fibrillation 100% NYHA class IV	**Intervention** MVIV with Braile Inovare implanted through cardiac apex **Comparator** None (NYHA class could be compared to baseline)	Success rate Postoperative mortality, 30-day and 1-year mortality, major cardiovascular events, 30-day and 1-year NYHA class, vascular complications, bleeding, cerebrovascular accident

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Mean STS score (%) 15.8 Mean EuroSCORE (%) 20.2		
Murzi et al. 2017[16] Spain Funding not reported	Retrospective cohort	**61 patients** undergoing reoperative mitral valve procedures for failed bioprostheses between 2005 and 2015 No exclusion criteria described **M-VIV** n=21, mean age 77, 62% female, 86% with NYHA class III or IV, 43% with history of atrial fibrillation, 9.5% with vascular disease, 14% with patent bypass graft, 90% with severe pulmonary hypertension (≥50 mmHg), mean EF 50%, mean EuroSCORE logistic 39 **MIMVR** n=40, mean age 67, 56% female, 71% with NYHA class III or IV, 10% history of atrial fibrillation, 15% with vascular disease, 17% with patent bypass graft, 34% with severe pulmonary hypertension (≥50 mmHg), mean EF 53%, mean EuroSCORE logistic 23	**Intervention = M-VIV** Transcatheter mitral valve-in-valve implantation performed via transapical approach; Sapien XT in 18 patients and Sapien 3 in 3 patients **Comparator = MIMVR** Minimally invasive mitral valve replacement performed through a lateral right minithoracotomy	In-hospital death, stroke, reoperation for bleeding, LCOS, pulmonary complications, ICU stay in days, hospital stay in days 2-year survival
D'Onofrio et al. 2016[30] Italy Funding not described	Case series	**22 patients** who underwent MVIV at five Italian institutions from January 2008 to May 2015 Patients were suffering from a malfunctioning previously implanted bioprosthesis and deemed **inoperable or at high risk for conventional surgery** for anatomic reasons or general clinical conditions or high predicted mortality rate (STS > 8% or EuroSCORE > 20%) **Exclusion criteria** Active endocarditis, paravalvular leak Mean age 76	**Intervention** MVIV via transapical approach using Sapien valve **Comparator** None (NYHA class could be compared to baseline)	**30 days** Mortality, cardiovascular mortality, MI, stroke NYHA at 1 year Survival at 3 years

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		27% male 100% in NYHA class III or IV 72% had systemic arterial hypertension, 23% peripheral vascular disease, 5% diabetes, 32% COPD, 73% atrial fibrillation Mean EuroSCORE I logistic (%) 32 Mean EuroSCORE II (%) 13.7 STS score (%) 12.2		
Nachum et al. 2016[29] Israel Funding not reported	Case series	**9 patients** undergoing MVIV implantation for failed mitral bioprostheses at one center in Israel Patients were considered **high risk for conventional redo mitral valve replacement** due to advanced age, comorbidities, or frailty Mean age 82 67% female 100% NYHA class III or IV 86% had hypertension, 100% hypercholesterolemia, 44% diabetes, 22% COPD, 22% GFR < 60 mL/min, 44% CHD, 33% previous stroke, 33% permanent atrial fibrillation, 44% previous CABG Mean EuroSCORE I (%) 25.5 Mean EuroSCORE II (%) 11 Mean STS Score (%) 12	**Intervention** Transapical MVIV procedure using Sapien valve **Comparator** None (NYHA class could be compared to baseline)	Success rate, stroke, major bleeding **Follow-up (mean 13 months)** Mortality, NYHA class
Ye et al. 2015[28] Canada Funding not reported	Case series	**31 patients** underwent transcatheter MVIV implantation between April 2007 and December 2013 at a single center	**Intervention** MVIV implantation using Cribier-Edwards equine, Sapien, and Sapien XT valves via transapical approach	Success rate, intraoperative Complications **Early clinical outcomes (30 days)**

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Patients had previous mitral valve replacement with bioprostheses and were deemed **too high risk for conventional redo valve replacement surgery** Mean age 79 42% male 23% had diabetes, 52% CAD, 42% previous CABG, 23% COPD, 32% CVA, 13% peripheral vascular disease 97% in NYHA class III or IV Median STS score (%) 9.7	**Comparator** None (NYHA class could be compared to baseline)	Life threatening bleeding, major bleeding, disabling stroke, mortality, MI, major vascular complications **>30 day outcomes** Life threatening bleeding, major bleeding, disabling stroke, mortality, MI, major vascular complications Long-term mortality NYHA class at 2 years, 4 years, 5 years, 6 years
Tricuspid valve-in-valve procedures				
Viotto et al. 2019[19] Brazil Funding not reported	Case series	**7 patients** who underwent transcatheter VIV procedure for treatment of a degenerated bioprosthesis in the tricuspid position at a single center between November 2015 and December 2017; all patients deemed **high or extreme risk for conventional approach** 3 patients had Ebstein's anomaly, 1 patient tetralogy of Fallot, 1 neonatal endocarditis, 1 with ventricular septal defect with double tricuspid lesion, 1 with rheumatic mitral and tricuspid Mean age 33 57% male Median previous sternotomies 3 5 patients had arrhythmia at baseline EuroSCORE II range 1.5 to 2.9	**Intervention** Transcatheter tricuspid VIV procedure using Brail Inovare using transapical access **Comparator** None (NYHA class could be compared to baseline)	Success rate, periprocedural complications, NYHA class at follow-up
Landes et al. 2017[20] Israel	Case series	**7 patients** who received TVIV between 2011 and 2016 at five centers in central Israel	**Intervention** TVIV procedure (4 cases with Sapien XT,	Success rate, periprocedural

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding not reported		In each case, standard reoperation was overruled due to **extremely high operative risk** Mean age 63 71% female Mean EuroSCORE II 13.6 86% in NYHA class III or IV 86% had atrial fibrillation, 57% severe pulmonary hypertension Indication for valve intervention was stenosis (3 patients), regurgitation (3 1 patient), mixed (3 patients) 6 out 7 patients had rheumatic TV pathology	3 cases with Sapien 3) via transfemoral or transatrial approach **Comparator** None (NYHA class could be compared to baseline)	complications (vascular complication **Follow-up (mean 8 months)** NYHA class, mortality, stroke
McElhinney et al. 2016[22] Austria, Belgium, Canada, France, Germany, Italy, Portugal, Saudi Arabia, Switzerland, United States Funding not reported	Case series with data collected from an international registry of institutions between 2008 to 2015 53 centers contributed to dataset	**156 patients** receiving tricuspid valve-in-valve implants within surgical bioprosthetic valves (**no explicit criteria provided for inclusion**) Mean age 40, sex not reported, 56% with congenital disease, 44% with acquired disease, 30% had other prosthetic valves, 38% had atrial fibrillation, 39% had an existing pacemaker; NYHA class I (2%), II (26%), III (50%), IV (21%); mean number of cardiac surgeries was 2, mean age of bioprosthesis was 7.4 years	**Intervention = TVIV** Transcatheter valve implantation within an existing surgical tricuspid valve bioprosthesis; either Melody (94 patients) or Sapien valves (58 patients; Sapien in 12 patients, Sapien XT in 41, Sapien 3 in 5); access via femoral vein, jugular vein, or right atrium **Comparator** None (NYHA class could be compared to baseline)	NYHA class at 30 days and long-term follow-up (median of 13 months after procedure) Included a formal statistical comparison of the proportion of patients in NYHA class I or II at 30 days and long-term follow-up compared to baseline
Ruparelia et al. 2016[21] Italy Funding not reported	Case series	**5 patients** who underwent transcatheter tricuspid VIV implantation for tricuspid bioprosthesis failure at once center between March 2015 and July 2015 Patients had intractable symptoms in spite of optimal medical therapy and were	**Intervention** Transcatheter tricuspid VIV implantation using Sapien 3 performed via transfemoral venous route **Comparator**	Success rate **30 days** Mortality, readmission, stroke, bleeding, MI NYHA class

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		considered **high risk for redo surgery** Descriptive statistics not calculated by authors Age range 49 to 75 80% female 60% had hypertension, 20% previous CABG, 80% atrial arrhythmia 1 patient noted as having congenital disease 100% NYHA class III or IV EuroSCORE logistic (%) range 3.8 to 16.2	None (NYHA class could be compared to baseline)	

CABG = coronary artery bypass graft; CAD = coronary artery disease; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; LCOS = low cardiac output syndrome; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MIMVR = mitral valve replacement through right anterior minithoracotomy; M-VIV or MVIV = transcatheter mitral valve-in-valve implantation; NYHA = New York Heart Association; SMVR = surgical mitral valve replacement (redo); STS = Society for Thoracic Surgeons; TMVR = transcatheter mitral valve-in-valve replacement; TVIV = tricuspid valve-in-valve implantation; VIV = valve-in-valve.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Review Using AMSTAR 2[11]

Item	Hu et al. 2018[14]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes (two databases searched but did not describe searching reference lists, grey literature, trial registries)
5. Did the review authors perform study selection in duplicate?	Unclear
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Unclear
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2.

Table 5: Strengths and Limitations of Non-Randomized Studies Using the Downs and Black checklist [12]

Item	Retrospective cohort		Single arm studies															
	Kamioka et al. 2018[15]	Murzi et al. 2017[16]	da Costa et al. 2020[17]	Keenan et al. 2020[23]	Okoh et al. 2020[24]	Whise-nant et al. 2020[18]	Yamashita et al. 2020[31]	Joseph et al. 2019[32]	Viotto et al. 2019[19]	Elmously et al. 2018[27]	Eleid et al. 2017[25]	Gaia et al. 2017[26]	Landes et al. 2017[20]	Donofrio et al. 2016[30]	McElhinney et al. 2016[22]	Nachum et al. 2016[29]	Ruparelia et al. 2016[21]	Ye et al. 2015[28]
Aim described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Outcomes described?	N	N	N	N	Y	Y	N	Y	N	N	Y	Y	N	N	Y	N	N	N
Patients described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y
Intervention described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Confounders described?	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Findings described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Estimates of the random variability?	N	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	NA	NA	NA
AEs reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lost to f/u described?	U	U	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	N
Probability for main outcomes given?	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	NA
Subjects asked representative?	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Subjects participating representative?	U	Y	Y	U	Y	Y	U	U	Y	Y	Y	Y	U	U	U	Y	Y	Y
Staff, facilities representative?	Y	Y	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Subjects blinded?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Attempt to blind those measuring?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Was data dredging made clear?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adjust for different lengths of f/u?	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Stats for main outcomes appropriate?[b]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance reliable?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Outcome measures valid and reliable?	U	U	U	U	Y	Y	Y	Y	U	U	Y	Y	U	Y	Y	U	U	Y
Recruitment from same population?	N	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Subjects recruited over same period?	N	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Randomized?[a]	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adequate adjustment for confounding?	N	U	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	NA

Item	Retrospective cohort		Single arm studies															
	Kamioka et al. 2018[15]	Murzi et al. 2017[16]	da Costa et al. 2020[17]	Keenan et al. 2020[23]	Okoh et al. 2020[24]	Whise-nant et al. 2020[18]	Yamashita et al. 2020[31]	Joseph et al. 2019[32]	Viotto et al. 2019[19]	Elmously et al. 2018[27]	Eleid et al. 2017[25]	Gaia et al. 2017[26]	Landes et al. 2017[20]	Donofrio et al. 2016[30]	McElhinney et al. 2016[22]	Nachum et al. 2016[29]	Ruparelia et al. 2016[21]	Ye et al. 2015[28]
Loss to f/u taken into account?	U	Y	U	Y	N	Y	Y	Y	Y	Y	Y	U	Y	Y	N	Y	Y	U

AE = adverse events; f/u = follow-up; N = No; NA = not applicable; U = unable to determine; Y = yes

[a] The item surrounding allocation concealment was deleted as none of the studies used randomization.

[b] Rated as "Yes" for single arm studies because descriptive statistics were used to report most outcomes, which was considered appropriate.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Systematic Review (Hu et al. 2018[14])

Outcome	Findings	Authors' Conclusions
In-hospital outcomes		
Technical success (%)	167/172 (97.1)	"Use of the TMVIV…procedure for degenerated mitral bioprostheses or failed annuloplasty rings is a highly feasible, safe, and effective technique for the treatment of either valve stenosis or regurgitation for those patients who are not candidates for repeat surgery...The TMVIV…procedure [is] associated with excellent short-term clinical outcomes…" (p. 516) "Comparisons with surgical mitral valve replacement were unavailable" (p. 512)
Death (%)	9/172 (5.2)	
Cardiovascular death (%)	5/172 (2.9)	
MI (%)	0/172 (0)	
Stroke (%)	3/172 (1.7)	
Bleeding (%)	15/172 (8.7)	
New arrythmia (%)	3/172 (1.7)	
Acute kidney injury (%)	7/172 (4.1)	
NYHA ≥ III (%)	57/57 (100) before procedure and 1/39 (3.6) after procedure* (P<0.001)	"NYHA function improved" (p. 512)
30-day outcomes		
Death (%)	11/147 (7.5)	"Long-term follow-up data were limited" (p. 512) "Larger clinical trials are required to determine the durability and long-term outcomes" (p. 516)
MI (%)	0/95 (0)	
Stroke (%)	3/95 (3.2)	
Thrombus (%)	3/95 (3.2)	
Device migration (%)	5/95 (5.3)	
Device failure (%)	1/95 (1.1)	
6-month outcomes		
Death (%)	16/85 (18.8)	"However, in our analysis the overall 6-month mortality was…18.5% for MVIV. Long-term follow-up data were limited" (p. 512) "Larger clinical trials are required to determine the durability and long-term outcomes" (p. 516)
MI (%)	0/53 (0)	
Stroke (%)	3/56 (5.4)	
Thrombus (%)	5/60 (8.3)	
Device migration (%)	7/60 (11.7)	
Device failure (%)	3/54 (5.6)	

MI = myocardial infarction; MVIV = transcatheter mitral valve-in-valve implantation; NYHA = New York Heart Association; TMVIV = transcatheter mitral valve-in-valve implantation.

Table 7: Summary of Findings of Included Non-randomized Studies With Comparison Groups

Study	Outcome	Description	Findings	Authors' Conclusions
Kamioka et al. 2018[15]	In-hospital death	Findings are presented as proportion (%) in **SMVR** group (n=59) **versus** proportion in **TMVR** group (n=62) "Categorical variables were examined using a chi-square test or Fisher exact test" (p. 1132) Outcome definitions not provided	3.4% versus 3.2% (P=1.00)	"There was no difference in mortality at 30 days and at 1 year between SMVR and TMVR patients despite higher risk in the TMVR patients" (p. 1137) "Although these findings need to be confirmed by long-term follow-up and larger study groups, our study suggests that TMVR is an option for patients with bioprosthetic mitral valve failure" (p. 1134)
	Major vascular complication		5.1% versus 1.6% (P =0.36)	
	Life-threatening bleeding		11.9% versus 6.5% (P=0.30)	
	Major bleeding		33.9% versus 8.1% (P<0.001)	
	Minor bleeding		11.9% versus 8.1% (P=0.49)	
	Major stroke		3.4% versus 0% (P=0.24)	
	New atrial fibrillation		30.5% versus 1.6% (P<0.001)	
	LVOT obstruction		0% versus 3.2% (P=0.16)	
	Prolonged ventilation (>24 hours)		33.9% versus 4.8% (P<0.001)	
	30-day mortality		3.4% versus 3.2% P=1.00)	
	1-year mortality		11.9% versus 11.3% (P=0.92)	
	Total ICU time, hours	Mean (SD) in **SMVR** group **versus TMVR** Compared using t test or Wilcoxon rank sum test	118 (129) versus 40 (43) (P<0.001)	
	Length of stay after procedure, days		10.6 (6.6) versus 6.3 (4.8) (P<0.001)	
Murzi et al. 2017[16]	In-hospital deaths	Findings are presented as proportion (%) in **MIMVR** group (n=40) **versus M-VIV** group (n=21) aOR[a] (95% CI) for outcome in **MIMVR versus M-VIV** (logistic regression with propensity score) Outcome definitions not provided	7.5% versus 4.7% aOR 2.46 (0.16 to 36.7)	"Our data set suggests that M-VIV is a safe, effective procedure. A trend towards better outcomes with M-VIV implantation was evident. Although operative therapy still represents the gold standard, transcatheter valve-in-valve implantation in malfunctioning mitral bioprostheses represents an excellent option for selected patients, thereby avoiding chest re-entry, cardiopulmonary bypass and cardioplegic arrest." (p. 61)
	Stroke		12.5% versus 4.7% aOR 0.89 (0.48 to 16.2)	
	LCOS		4.9% versus 4.7% aOR 0.44 (0.23 to 8.77)	
	Pulmonary complications		20% versus 9.4% aOR 1.13 (0.16 to 7.81)	
	Reoperation for bleeding		14.6% versus 4.7% aOR 0.43 (0.50 to 3.67)	
	ICU stay (days)	Mean days (SD) in **MIMVR versus M-VIV**; no statistical comparison	5 (4) days versus 3 (7) days	
	Hospital stay (days)		14 (7) days versus 9 (7) days	
	2-year survival	Proportion surviving in **MIMVR versus M-VIV**; statistical comparison using log-rank test	87.1% versus 86.1% (log-rank P=0.148)	

aOR = adjusted odds ratio; CI = confidence interval; ICU = intensive care unit; LCOS = low cardiac output syndrome; LVOT = left ventricular outflow tract; MIMVR = mitral valve replacement through right anterior minithoracotomy; M-VIV or MVIV = transcatheter mitral valve-in-valve implantation; NYHA = New York Heart Association; SD = standard deviation; SMVR = surgical mitral valve replacement (redo); TMVR = transcatheter mitral valve-in-valve replacement; TVIV = tricuspid valve-in-valve implantation.

[a] Adjusted for age, sex, NYHA class III or IV, diabetes mellitus, cerebrovascular disease, vascular disease, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney failure, ejection fraction (%), patent bypass graft, severe pulmonary hypertension, severe tricuspid regurgitation, EuroSCORE logistic

Table 8: Summary of Findings of Included Single Arm Studies and Case Series

Study	Definition	Findings	Authors' Conclusions
Mitral valve-in-valve procedures			
Success rate			
da Costa et al. 2020[17]	Successful TMVIV implantation (%) (authors mention adequate valve positioning and no need for cardiopulmonary bypass)	49/50 (98)	"TMVIV has proven to be a safe and effective procedure to treat bioprosthetic valve dysfunction in the mitral position… Nevertheless, there is a clear necessity for further long-term studies to evaluate the durability of the VIV procedure and for randomized controlled trials designed to compare TMVIV implantation and conventional surgical redo." (p. 234)
Keenan et al. 2020[23]	Procedure successful (%) defined as the absence of procedural mortality, the correct positioning of a single transcatheter prosthesis, and the absence of residual moderate or severe prosthetic regurgitation or stenosis	6/7 (86)	"Our early experience with transcatheter transseptal mitral valve-in-valve implantation demonstrates this procedure to be feasible in our institution with acceptable early results. Further follow-up is necessary to determine the longevity of valves implanted in this manner, especially in the younger population" (p. 921)
Okoh et al. 2020[24]	Procedural success (%) according to MVARC-2 definition	15/15 (100)	"Procedural outcomes were congruent with previous studies and demonstrated a 100% success rate with no evidence of valve malposition or embolization" (p. 52) "We have demonstrated that MVIV replacement is an acceptable treatment in select high-risk patients with degenerated bioprostheses." (p. 54)
Whisenant et al. 2020[18]	Technical success at exit from hybrid suite as per MVARC criteria (%)	1480/1529 (96.8)	"Transcatheter MVIV using the SAPIEN 3 was associated with high technical success" (p. E5)
Elmously et al. 2018[27]	Device success defined by MVARC-2 criteria	19/19 (100)	"Despite this patient cohort, TA-MVIV resulted in favorable early and midterm outcomes, with no deaths, strokes, or myocardial infarctions at 30 days, and a 1-year mortality rate of 5.2%." (p. 1782)
Eleid et al. 2017[25]	Procedural success (%) defined as absence of procedural mortality, correct positioning of valve, absence of residual moderate or severe prosthetic regurgitation or stenosis	58/60 (97)	"Antegrade transvenous transseptal balloon-expandable THV implantation for failed mitral bioprosthesis is associated with 97% acute procedural success, 95% 30-day survival, 86% 1-year survival, and durable prosthesis function at 1 year of follow-up" (p. 1940)
Gaia et al. 2017[26]	Procedrual success defined by correct position, satisfactory haemodynamic measures, lack of significant transvalvular	"Successful valve implantation was possible in all cases" (p. 517)	"Our present experience demonstrates the feasibility of Braile Inovare implantation in failed mitral surgical valves. The device offered an increased procedural success rate, technically simple implantation, satisfactory haemodynamics and excellent followup results for the observed period." (p. 518)

Study	Definition	Findings	Authors' Conclusions
	or paravalvular regurgitation, lack of interference with the left ventricular outflow tract and lack of major vascular complications (including conversion to conventional surgery)		"Further trials, especially if randomization is present, with larger numbers of patients are needed to explore in greater depth the longer term results and safety of this procedure." (p. 519)
Nachum et al. 2016[29]	Device success (%) as per MVARC-2 definition	9/9 (100)	"our study demonstrates that transcatheter transapical mitral valve-in-valve implantation for failed bioprosthesis is feasible in selected high risk patients" (p. 17)
Ye et al. 2015[28]	Procedural success (%) according to MVARC-2 definition	72/73 (98.6) for group of aortic (n=42) and mitral (n=31) ViV procedures (unsuccessful procedure appeared to be in aortic ViV procedure)	"Transcatheter VIV for failed surgical bioprostheses can be performed safely with a high success rate and minimal early mortality and morbidity." (p. 1735)
Mortality			
da Costa et al. 2020[17]	Intraoperative (%)	1/50 (2)	-
	30 days (%)	6/50 (12)	
Keenan et al. 2020[23]	30 days (%)	1/7 (14)	-
Okoh et al. 2020[24]	Procedural (%)	0/15 (0)	"In-hospital and 30-day mortality rates are strong indicators of surgical and technical success, so by achieving in-hospital and 30-day mortality rates of 0%, our study demonstrates the feasibility and efficacy of MVIV in high-risk patients" (p. 54)
	30 days (%)	0/15 (0)	
	1 year (%)	4/15 (27)	
Whisenant et al. 2020[18]	In-hospital mortality (%)	61/1529 (4)	"Transcatheter MVIV using the SAPIEN 3 was associated with…few complications, and 30-day mortality rates markedly lower than predicted by the STS score" (p. E5)
	30 days (%)	78 (5.4%)[a]	
	1 year (%)	175 (16.7%)[a]	
Yamashita et al. 2020[31]	At last follow-up (range 207-513 days)	Mortality not observed at last follow-up	"In the consecutive case series, the safe mitral valve-in-valve procedure was feasible." (p. 8)
Joseph et al. 2019[32]	During hospitalization (%)	0/13 (0)	"The primary observations of this cohort study are (1) initial procedural success rate with satisfactory mitral prosthesis function was high, (2) long-term survival was low due to the high risk nature of the population undergoing the procedure however in patients who survived the periprocedural period, mortality up until 4.5 years was low" (p. 1092) "Long-term outcomes on larger cohorts are needed…Prospective studies are warranted to evaluate efficacy and safety of mitral valve-in-valve therapy as percutaneous mitral valve replacement technology is developed." (p. 1094)
	30 days (%)	2/13 (15.4)	
	1 year (%)	25%*	
	Long-term follow-up (median 4.4 years) (%)	6/13 (46)	

Study	Definition	Findings	Authors' Conclusions
Elmously et al. 2018[27]	30 days	0/19 (0)	-
	Last follow-up (mean 339 days)	1/19 (5)	-
Eleid et al. 2017[25]	Periprocedural	2/60 (3)	-
	30 days	3/60 (5)	-
	1 year	14% (survival reported as 86%) [a]	-
Gaia et al. 2017[26]	Operative mortality	0/12 (0)	-
	Follow-up (median 612 days)	1/12 (8)	-
D'Onofrio et al. 2016[30]	30 days (%)	2/22 (9)	"Present findings confirm that transcatheter VIV is a safe and effective procedure for inoperable or high-risk patients suffering from mitral and/or bioprosthesis dysfunction needing reoperation. VIV provides good early and midterm clinical outcomes…the lack of prospective randomized data with longer follow-up suggests a cautious approach and therefore we believe that it should still be reserved to high-risk and inoperable patients" (p. 1972)
	3 years	9% (survival reported as 91%) [a]	
Nachum et al. 2016[29]	Procedural (%)	0/9 (0)	"There was no hospital mortality in our series" (p. 17)
	Follow-up (mean 13 months) (%)	0/9 (0)	"Taking into account the limitations of a mid-term follow-up period (13 ± 12 months)…no patient died during follow-up" (p. 17)
Ye et al. 2015[28]	30 day	0/31 (0)	"Our 30-day mortality following mitral VIV implantation was 0%." (p. 1741)
MI			
da Costa et al. 2020[17]	30 days (%)	2/50 (4)	-
Okoh et al. 2020[24]	30 days (%)	0/15 (0)	-
Whisenant et al. 2020[18]	Periprocedural (%)	5/1529 (0.3)	-
Elmously et al. 2018[27]	30 days (%)	0/19 (0)	-
Eleid et al. 2017[25]	"After the procedure"	0/60 (0)	-
D'Onofrio et al. 2016[30]	30 days	1/22 (4.5)	-
Ye et al. 2015[28]	30 days	0/31 (0)	-
	>30 days	0/31 (0)	
Stroke			
da Costa et al. 2020[17]	30 days (%)	1/50 (2)	-

Study	Definition	Findings	Authors' Conclusions
Keenan et al. 2020[23]	30 days (%)	0/7 (0)	-
Okoh et al. 2020[24]	30 days (%)	0/15 (0)	-
Whisenant et al. 2020[18]	Periprocedural (%)	10/1529 (0.7)	-
	30 days (n,%)	16 (1.1%)[a]	-
	1 year (n,%)	32 (3.3%)[a]	-
Elmously et al. 2018[27]	30 days (%)	0/19 (0)	-
Eleid et al. 2017[25]	"After the procedure"	0/60 (0)	-
Gaia et al. 2017[26]	Procedural (%)	1/12 (8.3)	-
D'Onofrio et al. 2016[30]	30 days (%)	0/22 (0)	-
Nachum et al. 2016[29]	Early stroke (%)	0/9 (0)	-
Ye et al. 2015[28]	Disabling stroke at 30 days (%)	1/31 (1.4)	-
	Disabling stroke > 30 days (%)	1/31 (1.4)	-
Major vascular complications			
da Costa et al. 2020[17]	30 days (%)	3/50 (6)	-
Keenan et al. 2020[23]	30 days (%)	0/7 (0)	-
Whisenant et al. 2020[18]	In-hospital (%)	21/1529 (1.4)	
Gaia et al. 2017[26]	Procedural (%)	1/12 (8.3)	-
Bleeding			
da Costa et al. 2020[17]	Major bleeding at 30 days (%)	2/50 (4)	-
Keenan et al. 2020[23]	Bleeding at 30 days (%)	1/7 (14)	-
Joseph et al. 2019[32]	Retroperitoneal bleeding requiring surgery (%)	1/13 (7.7)	-
Eleid et al. 2017[25]	Procedural major bleeding (%)	4/60 (7)	-
Nachum et al. 2016[29]	Early major bleeding (%)	1/9 (11)	-

Study	Definition	Findings	Authors' Conclusions
Ye et al. 2015[28]	Major bleeding at 30 days (%)	6/31 (8.2)	-
	Major bleeding at >30 days (%)	0/31 (0)	-
NYHA class			
da Costa et al. 2020[17]	NYHA class ≤ II (%)	95.4% at 30 days versus 20% at baseline	-
Keenan et al. 2020[23]	NYHA class I (%)	6/6 (100%) at 30 days versus 0/7 (0%) at baseline	-
Okoh et al. 2020[24]	NYHA class I/II (%)	15/15 (100%) at 30 days versus 3/15 (20%) at baseline	"At the time of the procedure, most patients (80%) who presented with NYHA III/VI functional status showed significant improvement at day 30" (p. 53)
Whisenant et al. 2020[18]	NYHA class I or II (%)	195/1510 (13%) at baseline versus 854/994 (86%) at 30 days	"Most patients experienced clinically important improvement in heart failure symptoms and quality of life by 30 days that were maintained at 1 year" (p. E5)
		195/1510 (13%) at baseline versus 318/352 (90%) at 1 year	
Yamashita et al. 2020[31]	Median NYHA class (range)	2 (1-3) at baseline and 1 (1-3) at 7 days	-
		2 (1-3) at baseline and 1 (1-2) at 30 days	
Joseph et al. 2019[32]	Mean (SD) NYHA class preimplant versus postimplant	3.5 (0.5) versus 1.9 (0.9) (P<0.01)	"In this small, high-risk cohort, the majority of patients experienced significant initial improvement in symptoms immediately after the Melody mitral valve-in-valve procedure, which was continued for 1 year for those available for follow-up." (p. 1093)
	Mean (SD) NYHA class at baseline versus 1 year	3.5 (0.5) versus 1.9 (0.8)	
	Mean NYHA class at baseline versus 3 years	3.5 (0.5) versus 1.8 (1.0)	
	Mean NYHA class at baseline versus 5 years	3.5 (0.5) versus 2.0 (0.8)	
Elmously et al. 2018[27]	NYHA class I or II at last follow-up (mean 339 days) compared to baseline	17/19 (89.5) versus 0/19 (0)	"From a functional standpoint, the majority of patients (18 of 19) were NYHA class I or II at 30-day follow-up." (p. 1782)
Eleid et al. 2017[25]	NYHA class at 1 year compared to baseline	18 (68%) NYHA class I, 8 (28%) NYHA class II, 1 (2%) NYHA class III	"At 1 year of follow-up, the majority of patients continued to experience improvements in functional status." (p. 1940)

Study	Definition	Findings	Authors' Conclusions
		versus 27 (45%) class III and 33 (55%) class IV at baseline	
Gaia et al. 2017[26]	NYHA class at 30 days compared to baseline	7 (58%) class I, 4 (33%) class II, 1 (8%) class III versus 12 (100%) class IV at baseline	-
	NYHA class at 1 year compared to baseline	6 (67%) class I and 3 (33%) class II versus 12 (100%) class IV at baseline	-
D'Onofrio et al. 2016[30]	NYHA class at 1 year compared to baseline	~65% NHYA class I, ~30% NYHA class II, ~5% class III at 1 year versus ~65% class III and ~35% class IV at baseline (estimated from figure; numerical data not provided)	"A significant improvement of NYHA functional class was observed at follow-up" (p. 1969)
Nachum et al. 2016[29]	NYHA class I or II at last follow-up (mean 13 months) compared to baseline	9/9 (100%) versus 0/9 (0%) at baseline	"In the present study and comparable series, all surviving patients experienced a significant improvement in NYHA functional class during follow-up." (p. 17)
Ye et al. 2015[28]	NYHA class I or II at 2 years versus baseline	100% versus 0% (only percentage given)	"Transcatheter VIV implantation provides significantly symptomatic relief and improved quality of life in the majority of patients with either aortic or mitral prosthetic disease" (p. 1742)
Other complications			
da Costa et al. 2020[17]	Sepsis at 30 days (%)	14/50 (28)	-
	Acute renal failure at 30 days (%)	15/50 (30)	
Keenan et al. 2020[23]	Acute kidney injury at 30 days (%)	1/7 (14)	-
	Readmission within 30 days (%)	1/7 (14)	-
	Transfusion within 30 days (%)	3/7 (43)	-
Okoh et al. 2020[24]	Acute kidney injury at 30 days (%)	1/15 (7)	-
	Readmission within 30 days (%)	0/15 (0)	-
	Respiratory failure (%)	1/15 (7)	-

Study	Definition	Findings	Authors' Conclusions
Whisenant et al. 2020[18]	New dialysis requirement at 30 days (n,%)	24 (1.7)[a]	
	New dialysis requirement at 1 year (n,%)	25 (1.8)[a]	-
Yamashita et al. 2020[31]	Adverse events at 30 days	"There were no major adverse events within 30 days after the procedure" (p. 4)	"In the consecutive case series, the safe mitral valve-in-valve procedure was feasible." (p. 8) "The long-term outcomes of the mitral valve-in-valve procedure are still unclear." (p. 7)
Joseph et al. 2019[32]	Acute kidney injury during hospitalization (%)	1/13 (7.7)	-
Elmously et al. 2018[27]	Postoperative cardiac arrest with complete cardiovascular and neurological recovery (%)	2/19 (10.5)	-
	Readmission at 30 days (%)	0/19 (0)	-
Gaia et al. 2017[26]	Procedural acute kidney injury (%)	0/12 (0)	-
D'Onofrio et al. 2016[30]	Acute kidney injury at 30 days	1/22 (4.5)	-
Ye et al. 2015[28]	Acute renal failure requiring hemodialysis at 30 days	1/31 (1.4)	-
Tricuspid valve-in-valve procedures			
Success rate			
Viotto et al. 2019[19]	Success	"The implant was successful in all cases, and there was no need for conversion to open surgery" (p. 60)	"In our experience, the implant was successful in all cases" (p. 62) "Transcatheter ViV implantation in the tricuspid position should be considered a safe and effective therapy in patients with structural valve degeneration and stands as a viable, reliable alternative for the treatment of degenerated bioprostheses in high-surgical risk/inoperable patients. In our case series of 7 consecutive patients, tricuspid ViV intervention proved to be an attractive alternative to redo conventional surgery, with clinical and haemodynamic improvement and no major complications. It is clear that further studies are necessary to improve the level of evidence and the quality of results for tricuspid ViV implantation. In this scenario, larger series and randomized clinical trials are needed." (p. 62)
McElhinney et al. 2016[22]	Success (%) defined as TVIV implanted in the intended location	150/152 (99)	"TVIV with commercially available transcatheter prostheses is technically and clinically successful in patients of various ages across a wide range of valve size." (p. 1582)

Study	Definition	Findings	Authors' Conclusions
			"ongoing data collection, patient follow-up, and further work are necessary to determine long-term valve function and to define specific risk factors for poor outcome" (p. 1592)
Ruparelia et al. 2016[21]	Successful implantation (%)	5/5 (100)	"This approach appears to be a safe and efficacious treatment alternative to redo surgery." (p. 1000)
Mortality			
Viotto et al. 2019[19]	Death during follow-up (mean 1.2 years)	0/7 (100)	"There were no deaths and no endocarditis during the 1.24 years of follow-up." (p. 62)
Landes et al. 2017[20]	Follow-up (mean 8 months)	1/7 (14)	"TVIV may be a safe and effective strategy to treat carefully selected patients with degenerated bioprosthetic tricuspid valve at high operative risk" (p. 156) "Although our follow-up time is limited, our findings of no major safety concerns, good post-TVIV device function and regression of symptoms point to TVIV as a highly reassuring treatment strategy…More studies with extended follow-up are needed to verify our results and to assess durability issues." (p. 159)
McElhinney et al. 2016[22]	30 days	5/152 (3)	-
	Follow-up (median 13 months)	17/152 (11)	-
Ruparelia et al. 2016[21]	30 days	0/5 (0)	-
MI			
Ruparelia et al. 2016[21]	30 days	0/5 (0)	-
Stroke			
Landes et al. 2017[20]	Follow-up (mean 8 months) (%)	1/7 (14)	-
Ruparelia et al. 2016[21]	30 days	0/5 (0)	-
Major vascular complications			
Landes et al. 2017	Peri-procedural (%)	1/7 (14)	-
Bleeding			
Ruparelia et al. 2016[21]	30 days	0/5 (0)	-
NYHA			
Viotto et al. 2019[19]	NYHA at follow-up (not specified) versus baseline	6 patients with NYHA class I and 1 patient with NYHA class II at follow-up versus 4 patients	-

Study	Definition	Findings	Authors' Conclusions
		with NYHA class II, 1 patient NYHA class III, 2 patients NYHA class IV at baseline	
Landes et al. 2017[20]	NYHA class at follow-up (mean 8 months) versus baseline	3 (50%) NYHA class I and 3 (50%) class II versus 1 (14%) class II, 2 (29%) class III, 4 (57%) class IV at baseline	"Six patients who underwent TVIV between 2014 and 2016 by a transfemoral approach experienced a significant improvement in their tricuspid valve function, accompanied by functional capacity progress and symptom relief soon after the implantation and during short to midterm follow-up" (p. 158-9)
McElhinney et al. 2016[22]	Proportion with NYHA class I or II at 30 days versus baseline	87% versus 28% (P<0.001)	"Most patients reported improvement in functional status" (p. 1589)
	Proportion with NYHA class I or II at last follow-up (median 13 months) versus baseline	85% versus 28% (P<0.001)	
	NYHA class at 30 days compared to baseline	4 patients class I and 1 patient class II at 30 days versus 4 patients class III and 1 patient class IV at baseline	"At 30-day follow up, all patients experienced significant symptomatic improvement" (p. 1000)
Other complications			
Viotto et al. 2019[19]	Postoperative acute kidney injury with no need for dialysis (%)	2/7 (29)	-
Ruparelia et al. 2016[21]	Acute kidney injury at 30 days (%)	1/5 (20)	-
	Readmission at 30 days (%)	0/5 (20)	-

aOR = adjusted odds ratio; CI = confidence interval; ICU = intensive care unit; LCOS = low cardiac output syndrome; LVOT = left ventricular outflow tract; MIMVR = mitral valve replacement through right anterior minithoracotomy; M-VIV or MVIV = transcatheter mitral valve-in-valve implantation; MVARC = Mitral Valve Academic Research Consortium; NYHA = New York Heart Association; SD = standard deviation; SMVR = surgical mitral valve replacement (redo); TA = transapical; TMVR = transcatheter mitral valve-in-valve replacement; TMVIV = transcatheter mitral valve-in-valve implantation; TVIV = tricuspid valve-in-valve implantation.

[a] Calculated from Kaplan-Meier curve so not possible to give proportion

Appendix 5: Further Information

Additional References

Single arm studies or case series with no pre-post comparison

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Irrelevant population (pools outcomes for patients receiving valve-in-valve procedures with other procedures)

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