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SUMMARY WITH CRITICAL APPRAISAL

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

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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
MIMVR	Mitral Valve Replacement Through Right Anterior Minithoracotomy
M-VIV	Transcatheter Mitral Valve-in-Valve Implantation
NYHA	New York Heart Association
SD	Standard Deviation
SMVR	Surgical Mitral Valve Replacement
TAVI	Transcatheter Aortic Valve Implantation
TMVR	Transcatheter Mitral Valve-In-Valve Replacement
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]

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.[4,5] 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.[5] 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] However, there appears to be 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

Three low-quality studies were retrieved surrounding the clinical effectiveness of aortic valves for degenerated mitral or tricuspid valve bioprostheses.

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 before-after study in patients with degenerated tricuspid valve bioprostheses reported that the proportion of patients in New York Heart Association Class I or II at 30 days and last follow-up after transcatheter valve-in-valve procedures increased compared to baseline (i.e., representing improved functional status). However, there was no comparison group in this study.

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

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. To generate higher-quality evidence, such studies should feature larger sample sizes and appropriate techniques to mitigate selection bias and bias due to confounding.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, 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 transcatheter valve-in-valve replacement using a transcatheter aortic valve and patients with a degenerated mitral or tricuspid bioprostheses. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and May 14, 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), 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, randomized controlled trials, non-randomized 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.

Critical Appraisal of Individual Studies

Non-randomized studies were appraised using the Downs and Black checklist.[6] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Quantity of Research Available

A total of 389 citations were identified in the literature search. Following screening of titles and abstracts, 362 citations were excluded and 27 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 24 publications were excluded for various reasons, and 3 publications[7-9] met the inclusion

criteria and were included in this report. Appendix 1 presents the PRISMA[10] 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

Three non-randomized studies were eligible.[7-9] The studies by Kamioka et al.[7] and Murzi et al.[8] were retrospective cohort studies and the study by McElhinney et al.[9] was a before-after study.

Country of Origin

The study by Kamioka et al.[7] was conducted in the United States, Murzi et al.[8] in Spain, and the study by McElhinney et al. was conducted at multiple centers (Austria, Belgium, Canada, France, Germany, Italy, Portugal, Saudi Arabia, Switzerland United States).[9]

Patient Population

The patient population in Kamioka et al. was patients with severely degenerated mitral valve prostheses.[7] There were 62 patients who received transcatheter mitral valve-in-valve replacement (TMVR), 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 New York Heart Association (NYHA) functional 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 study by Murzi et al., the patient population was those undergoing reoperative mitral valve procedures for failed bioprostheses.[8] There were 21 patients who underwent transcatheter mitral VIV implantation (M-VIV), 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.

The study by McElhinney et al. involved a group of 156 patients receiving tricuspid VIV implants within existing surgical bioprosthetic valves.[9] The mean age was 40 years. Sex was not described. Approximately 56% of patients had a congenital tricuspid valve disease, while 44% had an acquired disease. Around 30% had other prosthetic valves, 38% had atrial fibrillation, 39% had an existing pacemaker, the mean number of previous cardiac surgeries was two, and the mean age of the bioprostheses was 7.4 years. At baseline the proportion of patients within each NYHA functional class was: 2% class I, 26% class II, 50% class III, and 21% class IV.

Interventions and Comparators

In the study by Kamioka et al., the intervention was a balloon-expandable transcatheter heart valve (7 patients with Sapien, 14 with Sapien XT, 41 with Sapien 3) implanted via transapical or transseptal access (transcatheter mitral valve-in-valve replacement).[7] The comparator was surgical mitral valve replacement (SMVR) performed via standard sternotomy, thoracotomy, or minithoracotomy.

In Murzi et al., the intervention was transcatheter transapical mitral valve-in-valve implantation (M-VIV; 18 patients with Sapien XT and 3 patients with Sapien 3).[8] The comparator was minimally invasive mitral valve replacement through a right anterior minithoracotomy (MIMVR).

In McElhinney et al., all patients received transcatheter tricuspid valve implantation within an existing surgical bioprosthesis.[9] The procedures were done with either Melody (n=94) or Sapien (n=58; 12 patients with Sapien, 41 with Sapien XT, 5 with Sapien 3) valves.

Outcomes

Kamioka et al. 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.[7] 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.

Murzi et al. 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).[8] 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.

McElhinney et al. 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.[9] Change from baseline was measured using McNemar's test.

Summary of Critical Appraisal

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

Retrospective cohort studies

Both retrospective cohort studies[7,8] 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 the study by Kamioka et al.[7] did not provide measures of variability around between-group differences.

A central limitation in the study by Kamioka et al., was the presence of baseline imbalances between the two groups.[7] 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 study by Murzi et al., there were also baseline imbalances between study groups.[8] 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 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 M-VIV group in the Murzi et al. study), and neither provided any information about statistical power. Thus, it was unclear whether these studies had sufficient power to detect meaningful differences between groups. Kamioka et al.[7] 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 study by Murzi et al., there was wide variability around the effect estimates (wide 95% CIs), raising concerns around imprecision.[8]

The generalizability of the results in these studies was unclear. Kamioka et al. 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.[7] Kamioka et al. also noted that complex patients (those requiring CABG or double valve replacement) were excluded from their study, suggesting their results may not be applicable to complex patients. The study by Murzi et al. was conducted at a single center in Spain and the authors noted that the study encompassed the “initial learning curve” with M-VIV.[8] Thus, the extent to which the study results apply in the current routine care context, was unclear.

Before-after study

The study by McElhinney et al. clearly described the study aim, patient characteristics, intervention, and main findings.[9]

As this was a before-after study, the central limitation of this study was that there was no comparison group. Therefore, it was impossible to judge the comparative effectiveness of the transcatheter procedure relative to the surgical procedure from this study. Another limitation was that the data came from a voluntary registry, and the extent to which the cases in the registry represent those in the general patient population was not clear, which

raised concerns around potential selection bias and generalizability. Finally, the mean age of patients in this study was 40 years. Therefore, the extent to which the results were applicable to older persons was uncertain.

Summary of Findings

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

Clinical Effectiveness

Mitral valves

Kamioka et al. compared SMVR (surgery) to TMVR (transcatheter) for mitral valve-in-valve replacement.[7]

There was no significant difference between groups for the outcomes of in-hospital death (3.4% for SMVR versus 3.2% for TMVR, P=1.00), 30-day mortality (SMVR versus 3.2% for TMVR, P=1.00), or 1-year mortality (11.9% for SMVR versus 11.3% for TMVR, P=0.92).

Patients in the TMVR group had statistically significantly lower rates of new atrial fibrillation (30.5% for SMVR versus 1.6% for TMVR, P<0.001), prolonged ventilation for >24 hours (33.9% for SMVR versus 4.8% for TMVR, P<0.001), and major bleeding (33.9% for SMVR versus 8.1% for TMVR, P<0.001). The mean amount of time in the ICU (118 hours for SMVR versus 40 hours for TMVR, P<0.001) and length of stay after the procedure (10.6 days for SMVR versus 6.3 days for TMVR, P<0.001) were both significantly lower in the TMVR group.

The rates of life-threatening bleeding (11.9% for SMVR versus 6.5% for TMVR, P=0.30), major stroke (3.4% for SMVR versus 0% in TMVR, P=0.24), or vascular complications (5.1% for SMVR versus 1.6% for TMVR, P=0.36) were numerically lower in the TMVR group compared to the SMVR group, but these differences were not statistically significant.

The authors concluded that there appeared to be no difference in mortality between groups at 30 days and 1 year, which suggested that TMVR 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.

Murzi et al. compared MIMVR (surgery) to M-VIV (transcatheter) for mitral valve-in-valve replacement.[8] The authors reported crude event rates, as well as adjusted odds ratios (aOR).[8]

The rate of in-hospital deaths was not significantly different between groups (7.5% in the MIMVR group compared to 4.7% in the M-VIV group; aOR 2.46, 95% CI 0.16 to 36.7). Stroke occurred in 12.5% of the MIMVR group and 4.7% of the M-VIV group (aOR 0.89, 95% CI 0.48 to 16.2), while pulmonary complications occurred in 20% of the MIMVR group and 9.4% of the M-VIV group (aOR 0.16 to 7.81), both differences which were not statistically significant. The rate of reoperation for bleeding was 14.6% in the MIMVR group versus 4.7% in the M-VIV group (aOR 0.43, 95% CI 0.50 to 3.67), a difference which was not statistically significantly different. The mean ICU stay was 5 days (standard deviation [SD] 4 days) in the MIMVR group and 3 days (SD 7 days) in the M-VIV group, while the mean hospital stay was 14 days (SD 7 days) in the MIMVR group and 9 days (SD 7 days) in the M-VIV group. Differences in ICU and hospital stay were not compared statistically. The 2-year survival was 87.1% for the MIMVR group and 86.1% for the M-VIV group, which was not significantly different according to a log-rank test (P=0.148).

The authors concluded that M-VIV was safe and effective and that there was a trend towards better outcomes for M-VIV compared to surgery. They also suggested that M-VIV represented an option for select patients with malfunctioning mitral bioprostheses.

Tricuspid valves

McElhinney et al. followed a group of patients who received tricuspid VIV implants within surgical bioprosthetic valves.[9] They 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.

Cost-Effectiveness

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

The main limitation of the current evidence base was that there were few studies examining the clinical effectiveness of transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses, and no relevant economic evaluations. The studies included in this report were small (n=121, n=61, n=156) non-randomized studies, with serious methodological concerns. In particular, for transcatheter aortic valves for valve-in-valve replacement of tricuspid valves, only one before-after study was found and there was no evidence on comparative effectiveness versus surgery. The lack of evidence, and low-quality available evidence, makes it difficult to draw conclusions about the effectiveness of transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses.

One major challenge with observational clinical evidence in this context 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 patient characteristics; patients who received transcatheter approaches may not have been candidates for surgery). This created inherent concerns with selection bias and bias due to confounding 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.

The generalizability of the evidence to the Canadian context was difficult to establish. For mitral valves, there was no evidence in the Canadian context. One study was conducted at three centers in the US; however, the comparability of this population to the Canadian context was uncertain. For tricuspid valves, Canadian data were included in the registry; 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.

Another consideration was that the patients who received the surgical intervention in the Murzi et al. study all received minimally invasive surgery with minithoracotomy.[8] Conversely, the patients in the surgery group in the Kamioka et al. study received different surgical techniques (sternotomy, thoracotomy, minithoracotomy).[7] Therefore, the results

from Murzi et al. may only be relevant in contexts where the surgical option for this procedure involves minithoracotomy.

Conclusions and Implications for Decision or Policy Making

This report identified three non-randomized studies on transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses. Two retrospective cohort studies examined mitral valves, and one before-after study examined tricuspid valves. There was no evidence regarding the cost-effectiveness of transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses.

In patients with transcatheter aortic valves for degenerated mitral valve bioprostheses, one study concluded that there was no difference in mortality between a transcatheter approach and surgical replacement, while authors of the other study 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. 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. The length of time in the ICU and length of hospital stay were lower for patients who received a transcatheter procedure compared to those who received surgery in both studies (statistically significant in one study,[7] but no statistical comparison in the other). The authors of both studies suggested that transcatheter aortic valves for degenerated mitral bioprostheses were an option for select patients with failed bioprosthetic mitral valves.

In patients with transcatheter aortic valves for degenerated tricuspid valves, the proportion of patients with improved functional status (according to NYHA classification) increased at both 30 days and the last follow-up, compared to before the transcatheter procedure. The authors concluded 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, and concerns around lack of a comparison group in the before-after study. 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.[4,5,11]

As outlined in Appendix 5, there are a number of case series studies that examined the use of transcatheter aortic valves for degenerated mitral or tricuspid valve bioprostheses. While these studies did not provide information relevant to the current report since they did not include comparisons to surgical replacement or from baseline to follow-up after transcatheter aortic valve implantation, they may provide additional insight on this topic.

Given the limited evidence, 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. 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. 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 valves for 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). Finally, future studies should also investigate the cost-effectiveness of transcatheter aortic valves for degenerated mitral or tricuspid bioprostheses, as there is currently no evidence on this topic. 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.[4,5]

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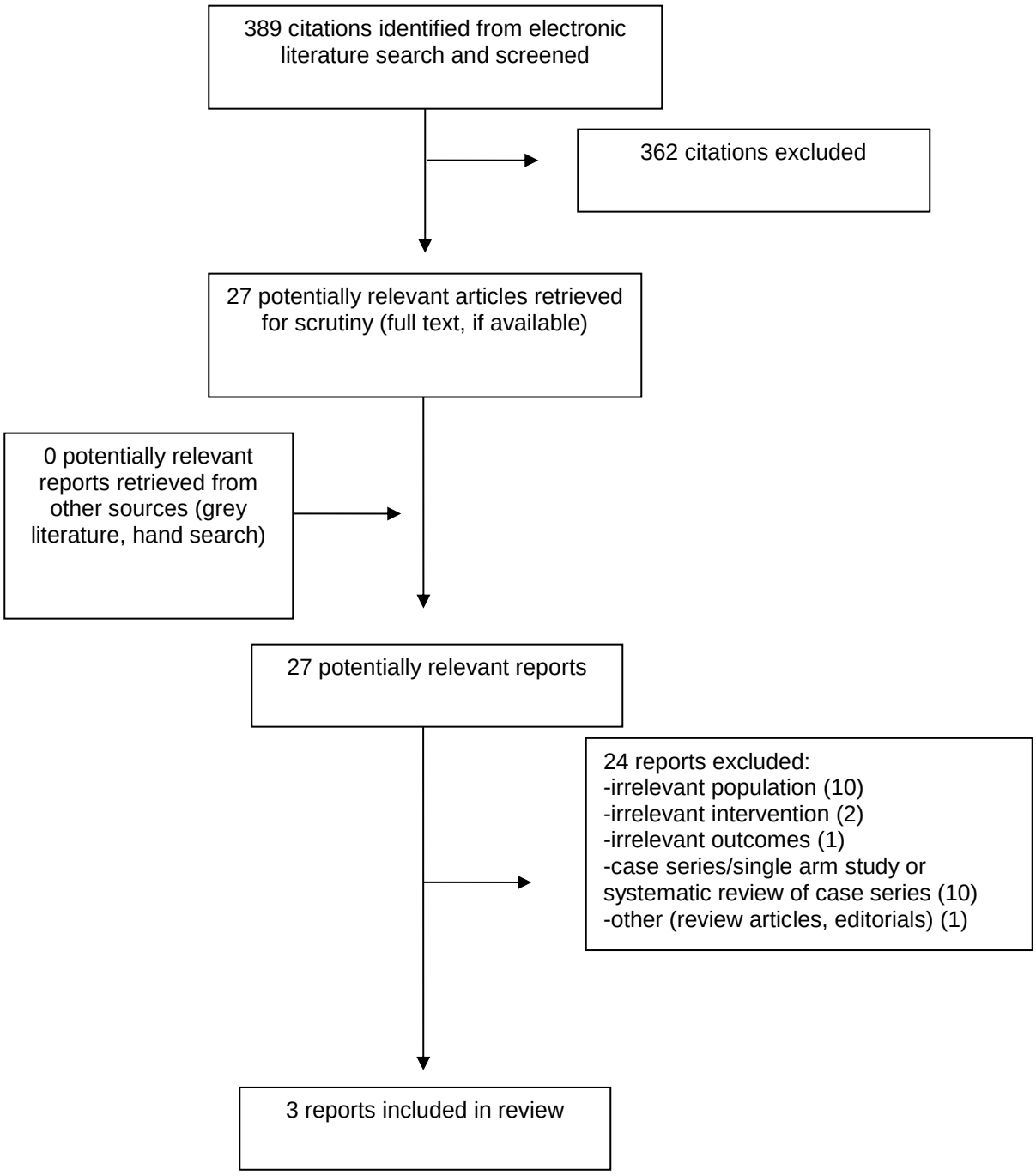
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: 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
Kamioka et al. 2018[7] 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
Murzi et al. 2017[8] Spain Funding not reported	Retrospective cohort	61 patients undergoing reoperative mitral valve procedures for failed bioprostheses between 2005 and 2015	**Intervention = M-VIV** Transcatheter mitral valve-in-valve implantation performed via transapical	In-hospital death, stroke, reoperation for bleeding, LCOS, pulmonary complications, ICU

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		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	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	stay in days, hospital stay in days 2-year survival
McElhinney et al. 2016[9] Austria, Belgium, Canada, France, Germany, Italy, Portugal, Saudi Arabia, Switzerland, United States Funding not reported	Before-after study 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 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) **Comparator = baseline** (pre-intervention)	Proportion with NYHA class I or II at 30 days and long-term follow-up (median of 13 months after procedure) compared to baseline

CABG = coronary artery bypass graft; 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 = transcatheter mitral valve-in-valve implantation; NYHA = New York Heart Association; SMVR = surgical mitral valve replacement (redo); TMVR = transcatheter mitral valve-in-valve replacement; TVIV = tricuspid valve-in-valve implantation.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Non-Randomized Studies Using the Downs and Black checklist[6]

Item	Kamioka et al. 2018[7]	Murzi 2017 et al. [8]	McElhinney et al. 2016[9]
Is the hypothesis/aim clearly described?	Yes	Yes	Yes
Are the main outcomes clearly described in the introduction or methods?	No	No	Yes
Are the characteristics of patients in the study clearly described?	Yes	Yes	Yes
Are the interventions of interest clearly described?	Yes	Yes	Yes
Are the distributions of principal confounders in each group of patients clearly described?	Yes	Yes	Yes
Are the main findings of the study clearly described?	Yes	Yes	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	No	Yes	No
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes	Yes
Have the characteristics of patients lost to follow-up been described?	Unclear	Unclear	No
Have actual probability values been reported for the main outcomes?	Yes	Yes	Yes
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unclear	Unclear	Unclear
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear	Yes	Unclear
Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Yes	Yes	Unclear
Was an attempt made to blind study subjects to the intervention they have received?	No	No	No
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	No	No
If any of the results of the study were based on data dredging, was this made clear?	No	No	No
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	Yes	N/A
Were the statistical tests used to assess the main outcomes appropriate?	No	Yes	Yes

Item	Kamioka et al. 2018[7]	Murzi 2017 et al. [8]	McElhinney et al. 2016[9]
Was compliance with the intervention(s) reliable?	Yes	Yes	Yes
Were the main outcome measures used accurate (valid and reliable)?	Unclear	Unclear	Yes
Were patients in different intervention groups recruited from the same population?	No	Yes	N/A
Were subjects in different intervention groups recruited over the same time period?	No	Yes	N/A
Were study subjects randomized to intervention groups?	No	No	No
Was the randomized intervention assignment concealed from patients and staff until recruitment was complete and irrevocable?	N/A	N/A	N/A
Was there adequate adjustment for confounding in the analyses from which main findings were drawn?	No	Unclear	Yes
Were losses to follow-up taken into account?	Unclear	Yes	No

N/A = not applicable.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Non-Randomized Studies

Study	Outcome	Description	Findings	Authors' Conclusions
Kamioka et al. 2018[7]	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" (*p1137*) "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" (*p1134*)
	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[8]	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." (*p61*)
	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)	

Study	Outcome	Description	Findings	Authors' Conclusions
McElhinney et al. 2016[9]	Functional status at 30 days	Proportion (%) with NYHA class I or II compared to baseline for patients receiving TVIV	87% at 30 days versus 28% at baseline (P<0.001)	"Most patients reported improvement in functional status" (*p1589*)
	Functional status at last follow-up (median 13 months after procedure)		85% at last follow-up versus 28% at baseline (P<0.001)	

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 = 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, and EuroSCORE logistic.

Appendix 5: Further Information

Additional References of Interest

Case series

Da Costa LPN, Palma JH, Barbosa Ribeiro H, et al. Transcatheter mitral valve-in-valve implantation: reports of the first 50 cases from a Latin American Centre. *Interact Cardiovasc Thorac Surg.* 2020 Feb;30(3): 229-235.

Taggart NW, Cabalka AK, Eicken A, et al. Outcomes of transcatheter tricuspid valve-in-valve implantation in patients with Ebstein anomaly. *Am J Cardiol*. 2018;121(2):262-268.

Elmously A, Worku B, Gray KD, Salemi A, et al. Mitral valve-in-valve Implantation as an elective or rescue procedure in high-risk patients. *Ann Thorac Surg.* 2018 Jun;105(6):1778-1783.

Single arm studies with no pre- and post-intervention comparisons

Guerrero M, Vemulapalli S, Xiang Q, et al. Thirty-day outcomes of transcatheter Mitral valve replacement for degenerated mitral bioprostheses (Valve-in-Valve), failed surgical rings (Valve-in-Ring), and native valve with severe mitral annular calcification (Valve-in-Mitral Annular Calcification) in the United States. *Circulation.* 2020;13(3):e008425.

Okoh AK, Shah A, Kang N, et al. Outcomes after transcatheter mitral valve-in-valve replacement in patients with degenerated bioprosthesis: a single-center experience. *J Invasive Cardiol.* 2020;32(2):49-54.

Yoon SH, Whisenant BK, Bleiziffer S, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. *Eur Heart J.* 2020;40(5):441-451.

Yoon SH, Whisenant BK, Bleiziffer S, et al. Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annuloplasty fings. *J Am Coll Cardiol.* 2017 Aug;70(9):1121-1131.

Urena M, Brochet E, Lecomte M, et al. Clinical and haemodynamic outcomes of balloon-expandable transcatheter mitral valve implantation: a 7-year experience. *Eur Heart J.* 2018;39(28):2679-2689.

Eleid MF, Whisenant BK, Cabalka AK, et al. Early Outcomes of Percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. *JACC Cardiovasc Interv.* 2017;10(19):1932-1942.

Systematic review involving case series and single arm studies

Flynn CD, Wilson-Smith AR, Yan TD, et al. Novel mitral valve technologies—transcatheter mitral valve implantation: a systematic review. *Ann Cardiothorac Surg* 2018;7(6):716-723.