



Transcatheter mitral valve replacement for degenerated mitral bioprostheses: a systematic review

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Background: Treatment of degenerated mitral bioprostheses with transcatheter mitral valve-in-valve (MVIV) implantation is increasingly used. The goal of this review was to evaluate the one-year outcomes of this therapy using the most recent evidence.

Methods: A MEDLINE, Cochrane database and SCOPUS search was performed of published observational studies involving patients undergoing transcatheter MVIV for degenerated bioprosthesis to determine procedural success, thirty-day and one-year survival.

Results: A total of 2,684 patients undergoing transcatheter MVIV were identified from five studies with mean age of 73–75 years, 57–63% female and Society for Thoracic Surgery (STS) risk score ranging from 9–13%. Procedural technical success ranged from 94–98%, with 1–3% rates of periprocedural death, 0–2% stroke and 1–5% risk of left ventricular outflow tract (LVOT) obstruction. Thirty-day post-procedure mean mitral prosthetic gradient ranged from 6–7 mmHg and residual mitral regurgitation was mild or less in 96–100% of patients. Thirty-day survival and one-year survival ranged from 93–97% and 83–89% respectively.

Conclusions: Transcatheter MVIV is an effective treatment for structural degeneration of biologic mitral valve replacement with low complication rates and favorable one-year outcomes. Accordingly, MVIV should be considered as a reasonable alternative to re-do surgical mitral valve replacement in high risk patients with comorbidities. Further study of long-term outcomes of this treatment is needed.

Keywords: Transcatheter; valve-in-valve; mitral



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Introduction

Mitral valve disease is one of the most common valvular heart diseases requiring intervention, and the prevalence increases with age (1). Mitral valve replacement is often required for severe mitral valve disease not amenable to repair, with patients frequently choosing a bioprosthesis over mechanical prosthesis to avoid the need for long-term anticoagulation (1). Over time, structural deterioration of mitral bioprostheses occurs due to immune-mediated inflammation and/or subclinical thrombosis in 35% of patients at ten years, with incidence increasing thereafter particularly in younger-aged patients (2). Repeat mitral

valve surgery carries an increased risk of morbidity and mortality (3), especially in older patients with comorbidities, prompting the need for less invasive alternatives. This clinical need, along with technological advancements in transcatheter valve replacement technology have driven significant innovations in mitral valve-in-valve (MVIV) therapy over the last decade since the first MVIV procedures (4-6) that will be discussed in this systematic review.

Methods

This systematic review is reported according to the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and followed an a priori established protocol (7). The quality of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (8).

Literature search strategy

We searched Ovid MEDLINE, Ovid CENTRAL, Ovid EMBASE, Cochrane Database and Scopus from database inception to October 13, 2020 using a combination of controlled vocabulary (subject headings) and text words. All languages and all ages were included. Specific key words included transcatheter mitral valve implantation, transcatheter mitral valve replacement, MVIV and degenerated mitral bioprosthesis. The detailed search strategy is available in supplementary file 1: <https://cdn.amegroups.cn/static/public/10.21037acs-2021-tviv-10-1.pdf>. In addition, the references of eligible articles and relevant citations were reviewed using Web of Science and Scopus.

Eligibility criteria

Observational studies of transcatheter MVIV using balloon-expandable transcatheter valves and either transapical or transeptal delivery approaches were included. We excluded: (I) single case reports, (II) case series of less than fifty patients, (III) studies without one-year clinical follow-up reported and (IV) studies not published in full-length manuscript format (abstract or letter only). In case of multiple studies from the same cohort, we only included data from the most recent comprehensive report. For MVIV reports that also included patients with prior mitral valve repairs including prior annuloplasty ring or band, these patients with prior repairs were not included and only patients with bioprosthetic mitral valves were analyzed.

Data extraction and critical appraisal

Citations were screened at the title and abstract level by one reviewer and retrieved as a full report if they reported data on outcomes after transcatheter MVIV. Data on the following study- and patient-related characteristics were independently evaluated by two reviewers: (I) study characteristics—primary author, time period of study/year of publication, geographic location of the population studied and study design; (II) characteristics—total number

of patients undergoing transcatheter MVIV, type and access route of transcatheter MVIV devices used; (III) Society for Thoracic Surgeon (STS) risk score (based on co-morbidities including previous coronary artery bypass grafting surgery, history of stroke, diabetes mellitus, chronic pulmonary disease and chronic kidney disease) and (IV) outcomes—one year all-cause or cardiovascular mortality. Two reviewers independently assessed the risk of bias of the included observational studies using the Newcastle-Ottawa instrument. This scale grades studies according to eight methodological criteria (9).

Statistical analysis

Continuous variables were reported as either mean \pm standard deviation or median (range) for skewed data. For each study we reported the proportion of patients undergoing transeptal versus transapical access, along with the mean percentage values for procedural technical success, thirty-day survival and one-year survival. Procedural technical success was similar among studies and was generally defined as successful device implanted in the correct position of the first intended device, with absence of intraprocedural mortality, emergency surgery or device retrieval. One study also included absence of moderate or more prosthetic regurgitation or stenosis in the procedural success definition. Mean \pm standard deviation transmitral gradient by echocardiography at thirty-days and one-year was reported. Compiled results among all studies were reported as a range.

Results

Quantity of evidence

A study selection process flowchart detailing the number of studies identified, evaluated and excluded is shown in *Figure 1*. A total of five studies were included in the final analysis, totaling 2,684 patients (10-14).

Quality of evidence

Study quality characteristics according to the Newcastle-Ottawa scale are shown in supplementary file 2: <https://cdn.amegroups.cn/static/public/10.21037acs-2021-tviv-10-2.pdf>. All the studies were observational multicenter registry studies and included full patient demographic data, procedural characteristics, thirty-day and one-year follow-

up outcomes.

Basic demographics

Baseline demographics of the patients in each study are shown in *Table 1*. Patient characteristics between studies were very similar, with a population mean age of 73–75 years, most patients being female and having a high mean STS risk score ranging from 9–13%. Notable differences in procedural characteristics included a varying range of access routes used

(transseptal *vs.* transapical) between studies (*Table 1*).

Assessment of primary and secondary endpoints

Intraprocedural results among the studies were similar and are summarized in *Table 2*. Procedural technical success ranged from 94–98%, with rates of periprocedural death 1–3%, stroke 0–2% and risk of left ventricular outflow tract (LVOT) obstruction 1–5%, which in most cases was mild in severity. Rates of conversion to open surgery and need for a second transcatheter valve were less than 1% in all studies.

Immediate and thirty-day post-procedure mean mitral prosthetic gradient ranged from 6–7 mmHg across the studies. Residual mitral regurgitation was mild or less in 96–100% of patients in the studies. thirty-day survival ranged from 93–97%, and one-year survival 83–89%. With respect to symptoms, one-year NYHA class was reported in two of the studies (10,13) and 90–96% of patients were NYHA class 2 or less.

When comparing outcomes using the transseptal versus transapical approach, lower mortality was observed with the transseptal approach at one year (HR 0.67, 95% CI: 0.47–0.97, $P=0.03$) in the largest study from the Transcatheter Valve Therapies Registry (13). In contrast, no difference in survival was observed according to access site in the second largest study from the Valve in Valve International Database (12).

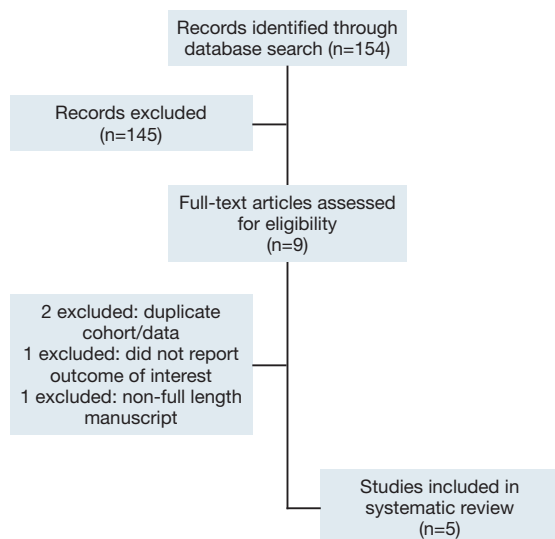


Figure 1 Flowchart demonstrating study selection for systematic review.

Discussion

The principal findings of this systematic review are that (I)

Table 1 Mitral valve in valve study characteristics

First author	Years of enrollment	N	Access type	Location	Age (yrs)	Female	STS score
Eleid	2014–2017	60	100% transseptal	Multicenter international	75±11	57%	13±8
Yoon	2015–2017	176	35% transseptal, 64% transapical	Multicenter international	73±13	63%	9±7
Kamioka	2012–2018	62	77% transseptal, 23% transapical	Multicenter US	75±9	61%	13±8
Whisenant	2015–2019	1529	87% transseptal, 13% transapical	Multicenter US	73 ±12	59%	11±9
Simonato	2006–2020	857	35% transseptal, 64% transapical	Multicenter international	74±13	59%	9 [5–14]
Range	2006–2020	60–1,529	35–100% transseptal, 0–64% transapical	NA	73–75	57–63%	9–13

STS, Society for Thoracic Surgeons; US, United States.

Table 2 Mitral valve in valve study outcomes

First author	Year	Procedural success	Procedural complications			Mean gradient (mmHg)	≤ mild MR	30-day survival	1 year survival
			Death	Stroke	LVOT obstruction				
Eleid	2017	97%	3%	0	5%	6±3	100%	95%	86%
Yoon	2017	96%	1%	2%	2%	6±3	96%	94%	87%
Kamioka	2018	98%	3%	0	3%	6±2	96%	97%	89%
Whisenant	2020	97%	2%	1%	1%	7±3	NR	95%	83%
Simonato	2020	94%	2%	1%	2%	6±3	97%	93%	86%
Range	2017–2020	94–98%	1–3%	0–2%	1–5%	6–7	96–100%	93–97%	83–89%

LVOT, left ventricular outflow tract; MR, mitral regurgitation; NR, not reported.

transcatheter MVIV therapy for degenerated bioprostheses is a safe and effective therapy with favorable thirty-day and one-year survival, (II) the transseptal approach is associated with lower complication rates and lower one-year mortality compared to transapical approach and (III) transcatheter MVIV is associated with mildly increased prosthesis mean gradients at one-year compared to surgery. These data support the utility of transcatheter MVIV for patients with degenerated mitral bioprostheses, particularly in those patients with comorbidities at high risk for redo mitral valve replacement surgery.

Initial experience and technique development for mitral valve in valve

The first series of successful transcatheter MVIV procedures performed via antegrade transseptal approach in patients with severe prosthesis dysfunction (either regurgitation, stenosis or a combination) utilized the bovine jugular vein balloon-expandable Melody (Medtronic, Minneapolis, MN, USA) valve typically used for transcatheter pulmonic valve implantation prior to the advent of transcatheter aortic valve replacement (15). This technique employed the use of left ventricular apical puncture to create a rail to provide support and facilitate coaxial valve deployment. Subsequent follow-up of these patients demonstrated that the majority did not require a redo mitral valve procedure and had satisfactory prosthesis function at a median follow-up of 4.4 years (16). Due to the inherent limitation of small diameter of the Melody valve, when the balloon-expandable SAPIEN (Edwards Lifesciences, Irvine, CA, USA) valve became available for use in aortic stenosis, the availability of larger sizes up to 29 mm made this the preferred

option for use in degenerated mitral bioprostheses. The initial published experience using the SAPIEN for MVIV included only surgical transapical access, reporting high procedural success and thirty-day survival rates (17). To avoid complications associated with transapical access, the transseptal approach was further developed without employing the use of a transapical or arteriovenous rail. This included the introduction of safer designed curved wires for use as a left ventricular rail from the transseptal approach and the use of smaller septostomy balloons to reduce the need to close the iatrogenic atrial septal defect (18,19). With these improved techniques, complication rates of transseptal MVIV at experienced centers became very low, facilitating rapid patient dismissal, favorable one-year outcomes (10) and ultimately the balloon-expandable SAPIEN valve received Food and Drug Administration approval in 2017 for MVIV therapy. A subsequent multicenter study compared outcomes of transcatheter MVIV with redo surgical mitral valve replacement and found no difference in one-year mortality between groups, despite the higher risk profile of the transcatheter MVIV group (11). Of note, mean mitral gradient was higher at one-year in the transcatheter group compared to the re-do surgical group (7.2 ± 2.7 vs. 5.5 ± 1.8 mmHg, $P=0.01$), suggesting an element of patient-prosthesis mismatch in the transcatheter group. The recent prospective Mitral Implantation of Transcatheter Valves trial of thirty patients undergoing MVIV using the latest transseptal techniques demonstrated a 100% technical success rate and a 96.7% one-year survival rate (20).

Mitral valve in valve large scale use and outcomes

Growing adoption of MVIV worldwide has afforded the

opportunity to study the outcomes over a broad experience in two recent large registry studies. Utilizing the STS/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry, outcomes of 1,529 patients undergoing transcatheter MVIV demonstrated technical success achieved in 97% of patients, with a thirty-day mortality of 5.4% despite a predicted risk of surgical mortality of 11.1%. In-hospital mortality was lower with transseptal access compared to transapical access (3.6% *vs.* 6.4%, $P=0.06$), which was primarily driven by lower cardiovascular death (1.8% *vs.* 4.4%, $P=0.03$) as well as a trend towards lower rates of major vascular complications and LVOT obstruction. one-year mortality in patients undergoing transcatheter MVIV was 16.7%, with lower mortality observed in patients with transseptal compared to transapical access (15.8% *vs.* 21.7%, $P=0.03$). Transcatheter MVIV was associated with improvements in NYHA class and mean gradient at one year was 7 ± 3 mmHg. Both one-year and mid-term outcomes of MVIV were subsequently examined in the Valve-in-Valve International Data Registry including 1,079 patients from 90 centers (12). In the MVIV population, technical success was achieved in 94% of patients, thirty-day mortality was 6.5% and one-year mortality was 13.8%. In longer term follow-up at four years, estimated mortality of the MVIV population was 37.5%. Importantly, mean valve gradient of ≥ 5 mmHg was present in 60% of MVIV patients immediately post procedure, suggesting a predisposition towards patient-prosthesis mismatch, and on average a 1 mmHg gradient increase was noted during the first one-four years of follow-up. Despite these elevated gradients, repeat mitral valve replacement rate was low at 1.9% over a four-year follow-up period.

Limitations

Despite the relatively large cumulative sample size of these studies and fairly complete one-year follow-up rates, they are limited by a lack of long-term follow-up and the observational nature of the data resulting in selection bias. No randomized studies exist comparing transcatheter MVIV to re-do surgical mitral valve replacement, and thus direct comparisons of the two treatments cannot be made with the available evidence. Given the high risk associated with redo surgical mitral valve replacement in the majority of patients experiencing structural degeneration of mitral bioprostheses, it is unlikely that an adequately powered randomized trial will be accomplished. Finally, the definition of procedural technical success also varied slightly according to studies,

which is a potential limitation of this analysis.

Conclusions

Transcatheter MVIV has become a safe and minimally invasive treatment for structural degeneration of biologic mitral valve replacement with favorable one-year outcomes. Transcatheter MVIV is associated with slightly higher mean gradients compared to re-do surgical mitral valve replacement at one-year despite favorable symptomatic status, and the long-term significance of this observation will require further study. Given the safety and effectiveness of transcatheter MVIV it should be considered as a reasonable alternative to re-do surgical mitral valve replacement, particularly for those at increased surgical risk. Further longitudinal studies are needed to assess long-term outcomes and understand the significance of patient-prosthesis mismatch in this population.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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