NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis

When the mitral valve in the heart does not work properly it may be replaced with a bioprosthetic artificial valve (made of biological tissue) through open heart surgery. If a bioprosthetic valve subsequently fails, another valve can be placed inside the first valve using a tube (catheter) inserted through a cut in the chest wall and then through the wall of the heart (transapical). The aim is to replace the faulty valve without needing repeat open heart surgery.

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Abbreviations

Word or phrase	Abbreviation
Confidence interval	CI
Hazard ratio	HR
Interquartile range	IQR
Left ventricular ejection fraction	LVEF
Left ventricular outflow tract obstruction	LVOT
Mitral Valve Academic Research Consortium	MVARC
Mitral valve replacement	MVR
Mitral regurgitation	MR
Not reported	NR
New York Heart Association	NYHA
Odds Ratio	OR
Patient prosthesis mismatch	PPM
Standard deviation	SD
Transcatheter mitral valve-in-valve implantation	TMVIV
Transcatheter mitral valve-in-ring	TMVIR
Transcatheter mitral valve-in-valve implantation	TMVIV
Transapical	TA
Transeptal	TS
Society of Thoracic Surgeons	STS
Valve-in-mitral annular calcification	VIMAC

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2020.

Procedure name

- Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis

Professional societies

- The Society for Cardiothoracic Surgery in Great Britain and Ireland
- British Cardiovascular Intervention Society.

Description of the procedure

Indications and current treatment

Mitral valve replacement is where an artificial prosthetic valve (bioprosthetic or mechanical) is inserted by open heart surgery. It is most commonly done for severe symptomatic mitral regurgitation but may also be done in patients with severe mitral valve stenosis or a combination of both. Symptoms of severe mitral valve disease typically include shortness of breath, fatigue and palpitations (because of atrial fibrillation).

Bioprosthetic valves have some advantages over mechanical valves, but they are more likely to degenerate and fail over time. This can result in severe stenosis or regurgitation, needing replacement of the bioprosthetic valve.

The standard treatment for a failed bioprosthetic valve is repeat open heart surgery to replace the valve. Repeat open heart surgery is associated with a higher risk of morbidity and mortality than primary surgery. Transapical transcatheter mitral valve-in-valve implantation is a less invasive alternative when repeat open heart surgery is considered to have a high risk. It avoids the need for routine cardiopulmonary bypass and can be used to treat failed bioprosthetic mitral valves originally placed during open heart surgery.

What the procedure involves

The procedure is done with the patient under general anaesthesia and using imaging guidance including fluoroscopy, angiography and transoesophageal

echocardiography (TEE). Prophylactic antibiotics and anticoagulants are given before and during the procedure. Temporary peripheral extracorporeal circulatory support (usually through the femoral vessels) is sometimes used.

The mitral valve is accessed surgically through an apical puncture of the left ventricle using an anterior or left lateral minithoracotomy (transapical approach). A guidewire is placed across the existing mitral prosthetic valve and into a pulmonary vein. A balloon catheter delivery system is then advanced over the guidewire. When there is severe prosthetic mitral valve stenosis a balloon valvuloplasty may be done first. The inner diameter of the degenerated valve is measured using TEE to establish the size of the new bioprosthetic valve needed. Using the delivery system, the new bioprosthetic valve is then introduced, manipulated into position and slowly deployed within the degenerated mitral valve under fluoroscopic and TEE guidance. Often rapid ventricular pacing is used to reduce movement of the heart. After valve deployment, the catheter delivery system, guidewires and pacing wires are removed and the left ventricular puncture and chest incisions are closed. Valve performance is then assessed using echocardiography and fluoroscopy.

Outcome measures

Clinical assessment tools

New York Heart Association (NYHA) heart failure classification. This is used to classify severity of breathlessness, from class 1, in which the patient has no limitation in daily physical activity, to class 4, in which the patient is breathless at rest.

The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) measures patient risk at the time of surgery using a logistic-regression equation on a 0 to 100% scale (higher scores indicating greater risk; a score higher than 20% indicates very high surgical risk).

Assessment of mitral valve function is usually made using echocardiography and Colour Flow Doppler:

- Mitral valve area (MVA; cm^2) or mitral valve area index (relative to body surface area; cm^2/m^2): a mitral valve area less than 0.6 cm^2/m^2 indicates severe mitral stenosis; 4 to 6 cm^2 is graded as normal, less than 1.0 is severe, 1.0 to 1.5 is moderate and more than 1.5 is mild stenosis.
- Transvalvular gradient (mmHg): mean transvalvular valve gradient more than 10 mmHg indicates severe mitral stenosis (5 to 10 mmHg is moderate stenosis, and less than 5 mmHg is mild stenosis).

- Severity of mitral regurgitation is graded as follows:
  - mild (grade 1+)
  - moderate (grade 2+)
  - moderately severe (grade 3+)
  - severe (grade 4+).

Efficacy summary

Technical success

In a systematic review of 245 patients with transcatheter mitral valve-in-valve implantation (TMVIV, in 172 patients) for degenerated mitral bioprosthetic valves or transcatheter mitral valve-in-ring implantation (TMVIR, in 73 patients) for failed annuloplasty rings, the overall technical success rate was 94% (229/245). The TMVIV procedure was associated with a higher technical success rate (97%, 167/172) than the TMVIR procedure (85% [62/73], p=0.001). The reported data which was pooled from patients who had the valve replacement using 2 different access routes (either transapical [TA] or percutaneous transeptal [TS]) showed a high technical success rate (TMVIV TA 99% [93/94] versus TS 95%, [58/61], p=0.337; TMVIR TA 90% [35/39] versus TS 87% [26/30], p=0.427). There was a high technical success rate in both groups with different mitral valve failure modes (mitral regurgitation [MR] or mitral stenosis [MS]; TMVIV MR 94%, [50/53] versus MS 100% [35/35]; p=0.405; TMVIR MR 86% [6/43] versus MS 93% [13/14]; p=0.837). Five technical failures happened in the TMVIV group (2 were because of technical operative error and 3 were because of prosthesis migration: 2 into the left atrium and 1 into the left ventricle) and 13 happened in the TMVIR group (Hu 2018).

In a retrospective registry analysis of 1,079 patients (from the Valve-in-Valve International Data Registry) with TMVIV implantation for degenerated mitral bioprosthetic valves (in 857 patients) and TMVIR for failed surgical repairs with annuloplasty rings (in 222 patients), the overall technical success rate was 91%. The TMVIV procedure was associated with higher technical success rate than TMVIR (TMVIV 94% versus TMVIR 82%; p<0.001). Technical success was defined as exit from catheterisation laboratory by MVARC criteria (absence of procedural mortality; successful access, delivery, and retrieval of the device delivery system; successful deployment of the first intended device; and freedom from emergency surgery or reintervention related to the device or access procedure; Simonato 2020).

In a retrospective registry analysis of 903 patients (from the Transcatheter Valve Therapy Registry) with TMVIV implantation for degenerated mitral bioprosthetic

valves (in 680 patients), TMVIR for failed surgical repairs with annuloplasty rings (in 123 patients) and transcatheter valve for severe mitral annular calcification (TVIMAC, in 100 patients), the overall technical success rate was 88% (793/902). The TMVIV procedure was associated with higher technical success rate followed by TMVIR and TVIMAC (TMVIV 91% [617/679], TMVIR 83% [102/123], TVIMAC 74% [74/100]; p<0.001). Technical success was defined as exit from catheterisation laboratory by MVARC criteria (absence of procedural mortality; successful access, delivery, and retrieval of the device delivery system; successful deployment of the first intended device; and freedom from emergency surgery or reintervention related to the device or access procedure; Guerrero 2020).

In a retrospective registry analysis of 521 patients (from the Transcatheter Mitral Valve Registry) with TMVIV implantation for degenerated mitral bioprosthetic valves (in 322 patients), TMVIR for failed surgical repairs with annuloplasty rings (in 141 patients) and TMV for severe annular calcification (TVIMAC, in 58 patients), the overall technical success rate was 87% (454/521). TMVIV had the highest success rate (94% [304/322]), followed by TMVIR and TVIMAC (81% [114/141] versus 62% [36/58]; p<0.001; Yoon 2019).

Device success

The retrospective registry analysis of 1,079 patients reported an overall device success rate of 39%, with a lower rate in the TMVIR group (TMVIV 41% versus TMVIR 32%; p=0.01). Device success was defined as absence of procedural mortality or stroke; proper placement and positioning of the device, freedom from unplanned surgical or interventional procedures related to the device or access procedure, continued intended safety and performance of the device, including no evidence of structural or functional failure, no specific device-related technical failure issues and complications; and reduction of mitral regurgitation to either optimal or acceptable levels without significant mitral stenosis (that is, post-procedure effective regurgitant orifice area is 1.5 cm^2 or more with a trans-mitral gradient less than 5 mmHg), and with no greater than mild (1+) paravalvular MR (and without associated haemolysis). With a modified definition of device success (that is, an immediate post-procedural mean gradient 10 mmHg or more), TMVIV still had better rates of device success (TMVIV 84% versus TMVIR 63%; p<0.001). After excluding the haemodynamic component of the success definition (that is, residual stenosis or regurgitation), success rates were 93% in TMVIV and 82% in TMVIR (p<0.001; Simonato 2020).

The retrospective analysis of 903 patients reported an overall device success rate of 94% (849/902) during the procedure, with a higher rate in TMVIV and TMVIR groups followed by TVIMAC group (TMVIV 95% [646/680], TMVIR 94% [115/123], and TVIMAC 88% [88/100]; p<0.001). At 30-days follow up, overall

device success rate was 79% (n=485), with a higher rate in TMVIV group followed by TMVIR and TVIMAC groups (TMVIV 84% [n=386], TMVIR 68% [n=58], and TVIMAC 59% [n=41]; p<0.001). Device success at 30 days was defined as absence of procedural mortality or stroke; freedom from unplanned surgical or interventional procedures related to the device or access procedure; and no residual mitral regurgitation greater than 1 (Guerrero 2020).

The retrospective registry analysis of 521 patients reported that device success was higher in the TMVIV group followed by TMVIR and TVIMAC groups (85% [273/322] versus 70% [98/141] versus 53% [31/58]; p<0.001; Yoon 2019).

Procedural success

The retrospective registry analysis of 903 patients reported procedural success in 71% (n=445) of patients at 30-days follow up. Rates were higher in TMVIV group and lower in TMVIR and TVIMAC groups (TMVIV 76% [n=359], TMVIR 60% [n=50], and TVIMAC 49% [n=36]; p<0.001). Procedural success is a composite of safety and efficacy end points defined as device success and absence of major clinical complications including: death, stroke, life-threatening bleed (by Valve Academic Research Consortium scale), major vascular complications, new stage 2 or 3 acute kidney injury including dialysis, myocardial infarction and absence of device-related dysfunction, migration, thrombosis, or other complications requiring surgery or repeat intervention (Guerrero 2020).

The retrospective registry analysis of 521 patients reported that procedural success was highest in the TMVIV group followed by the TMVIR and TVIMAC groups (74% [237/322] versus 57% [81/141] versus 41% [24/58]; p<0.001) (Yoon, 2019).

In a case series of 23 patients having TMVIV for degenerated mitral bioprosthetic valves, the procedure was successful in 100% of patients. Procedural success was defined according to Valve Academic Research Consortium 2 definition (device success and no occurrence of in-hospital or 30-day death). In 1 procedure, implantation via the left atrium through a right thoracotomy was unsuccessful (because the delivery system failed to align properly) but was successfully done through a left thoracotomy and transapical approach (Cheung 2013, 2011).

Symptomatic improvement

In the systematic review of 245 patients, there was significant improvement in NYHA functional class 3/4 after the procedure (overall, from baseline 98% [165/168] to 6% post-procedure [7/113]; p<0.001); TMVIV from baseline 97% [108/111] to 8% post-procedure [6/74], p<0.001) and TMVIR from baseline 100%

[57/57] to 3% post-procedure [1/36], p<0.001). No significant differences were found in NYHA outcomes in those with different mitral valve access routes (TMVIV TA 94% [46/49] versus TS 100% [12/12]; p>0.999; TMVIR TA 100% [18/18] versus TS 93% [14/15]; p=0.455) and between patients who had different mode of failures (TMVIV MR 94% [33/35] versus MS 100% [14/14]; p>0.999; TMVIR MR 95% [18/19] versus MS 100% [9/9]; p>0.999; Hu 2018).

The retrospective registry analysis of 903 patients reported there was significant improvement in NYHA functional class after the procedure. Before treatment, most patients were in NYHA class 3/4 (overall 90% [801/903], TMVIV 91% [n=611], TMVIR 88% [n=105], TVIMAC 86% [n=85], p=0.155). At 30-days follow up, fewer patients were in NYHA functional class 3 or more (overall 18% [n=86], TMVIV 16% [n=57], TMVIR 18% [n=12], TVIMAC 36% [n=17]). Most patients were in NYHA class 1 or 2 (overall 82% [n=389], TMVIV 84% [n=305], TMVIR 82% [n=54], TVIMAC 64% [n=30]; p=0.007; Guerrero 2020).

In the case series of 23 patients there was improvement in NYHA functional class after the procedure. Before treatment, 96% (22/23) of the patients were in NYHA class 3/4 and 1 patient was in class 2. At last follow up (range 376 days to 1,119 days), 96% (22/23) of the patients had clinically improved to NYHA class 1/2. One patient with hypertrophic obstructive cardiomyopathy continued to be in NYHA class 3 despite satisfactory valve function and septal ablation (Cheung 2013, 2011).

Transvalvular gradient

In the systematic review of 245 patients, the mean transmitral gradient after both procedures decreased significantly (TMVIV from 12.8±5.9 mmHg [n=121] to 5.1±2.5 mmHg [n=96], p<0.001; TMVIR from 9.5±5.2 [n=34] to 5.1±2.5 [n=44], p<0.001). No statistically significant differences were found in those with different mitral valve access routes (TMVIV TA 5.1±3.1 [n=39] versus TS 5.4±2.5 [n=43], p=0.652; TMVIR TA 4.3±2.3 [n=19] versus TS 5.9±2.6 [n=21], p=0.071) and between patients who had different mode of failures (TMVIV MR 5.6±2.7 [n=45] versus MS 5.0±3.2 [n=28], p=0.378; TMVIR MR 4.2±1.9 [n=21] versus MS 6.7±2.4 [n=15], p=0.002; Hu 2018).

In the retrospective analysis of 1,079 patients, an immediate post-procedural mean gradient more than 5 mmHg was reported in 61% of all patients, including 68% of TMVIR and 60% of TMVIV patients (p=0.05). The post-procedural mean mitral valve gradient decreased from baseline (overall from 10.7 to 5.7 mmHg, TMVIV from 11.4 to 5.6 mmHg [p<0.001]; TMVIR from 7.8 to 6.0 mmHg [p<0.001]). There was no significant difference between the groups (p=0.08). At 1-year follow up, a slight but statistically significant increase was reported in the

TMVIV group (6.7 mmHg, p<0.001) but not in the TMVIR group (6.5 mmHg, p=0.20; Simonato 2020).

The retrospective analysis of 903 patients reported that the post-procedural mean mitral valve gradient decreased from baseline and were similar in all groups (overall from 11 to 4 mmHg, TMVIV from 12 to 4 mmHg; TMVIR from 7 to 4 mmHg; TVIMAC 11 to 4 mmHg). At 30-day follow up, the median mean mitral valve gradient was 7 mmHg across TMVIV and TMVIR groups and 6 mmHg in the TVIMAC group (p=0.014; Guerrero 2020).

A retrospective comparative case series of 121 patients with degenerated bioprosthesis who had transcatheter mitral valve-in-valve replacement (TMVIV, n=62, via transapical [n=14] and transeptal [n=48] routes) compared with redo surgical mitral valve replacement (SMVR, n=59) reported that mean mitral valve pressure gradient was similar between the 2 groups (7.1±2.5 mmHg versus 6.5±2.5 mmHg; p=0.42) at 30 days. At 1-year follow up, the mitral valve pressure gradient was higher in the TMVIV group (TMVIV 7.2±2.7 versus SMVR 5.5±1.8; p=0.01; Kamioka 2018).

A retrospective comparative case series of 61 patients with degenerated bioprosthesis who had transapical TMVIV (n=21) compared with right anterior minithoracotomy mitral valve replacement (MIMVR, n=40) reported that mean mitral valve pressure gradient was 5.5±2.1 mmHg in patients who had TMVIV and 5.8±3.1 mmHg in patients who had MIMVR (p=0.74) at discharge (Murzi 2017).

A case series of 50 patients who had transapical TMVIV implantations reported that maximum and mean mitral gradients decreased from 23.5 to 14.6 mmHg and 11.5 to 6.4 mmHg postoperatively (da Costa 2020).

In the case series of 23 patients, there was a significant decrease in the mean mitral transvalvular gradient after implantation (from 11.1±4.6 mmHg to 6.9±2.2 mmHg, p=0.014; Cheung 2013, 2011).

Mitral valve area

The retrospective registry of 1,079 patients reported significant increases in mitral valve area for both TMVIV and TMVIR groups after the procedure (TMVIV from baseline 1.41 to 2.01 cm^2, p<0.001; TMVIR from baseline 1.87 to 2.13 cm^2, p=0.03) and remained stable during 1-year follow up (TMVIV 2.00 cm^2, p=0.85; TMVIR 1.99 cm^2, p=0.40; Simonato 2020).

Left ventricular ejection fraction (LVEF)

The retrospective registry of 1,079 patients reported that post-procedural LVEF decreased from baseline in both the TMVIV and TMVIR groups and was lowest in the TMVIR group (TMVIR 45.2±15.4% versus TMVIV 53.8±11.4% p<0.001) (Simonato 2020).

The retrospective registry of 521 patients reported that post-procedural LVEF remained lowest in the TMVIR group compared with the TMVIV and TVIMAC groups (44.4±14.7% versus 53.3±12.5% versus 58.0±11.5%; p<0.001; Yoon 2019).

Mitral regurgitation (MR) severity

In the retrospective registry analysis of 1,079 patients, there were significant post-procedure decreases in MR severity after both TMVIV and TMVIR procedures. The distribution of MR severity remained stable during 1-year follow up after TMVIR procedures (p=0.48), but the proportion of moderate MR increased at 1-year follow up in the TMVIV group (p=0.02; Simonato 2020).

In the case series of 23 patients, mitral regurgitation reduced from severe or moderate regurgitation (in 61% [14/23] and 17% [4/23] of patients respectively) at baseline to mild or trivial regurgitation (in 52% [12/23] and 48% [10/23] of patients respectively) at discharge; Cheung 2013, 2011).

Survival

In the systematic review of 245 patients, no significant differences in overall survival curves were seen for patients with different failure modes (MR or MS, p=0.347) and different access routes in the TMVIV procedure (TA or TS p=0.450). Similarly, no significant differences in overall survival curves were seen for patients with different failure modes (MR or MS, p=0.958) and different access routes in the TMVIR procedures (TA or TS, p=0.361; Hu 2018).

In the retrospective registry analysis of 1,079 patients, 1-year survival was significantly higher in patients who had TMVIV than those who had TMVIR (86% versus 77%, p=0.004). At 4 years follow up, TMVIV patients had significantly higher survival than TMVIR patients (63% versus 50%, p=0.002). Patients at high risk for repeat open heart surgery (STS score 8% or more) also had significantly worse survival at 4 years follow up (TMVIV 67% versus TMVIR 54%, p<0.001; Simonato 2020).

The retrospective comparative case series of 61 patients reported that the 2-year survival rates were 86±1% versus 87±1% in patients having TMVIV compared with those having MIMVR implantation, respectively (p=0.148; Murzi 2017).

In the case series of 23 patients, survival at 30 days follow up was 100%. At a median follow up of 753 days (range 376 days to 1,119 days), survival rate calculated using Kaplan–Meier analysis was 90% (Cheung 2013, 2011).

Procedure outcomes (time, intensive care unit stay, hospital stay)

The retrospective comparative case series of 121 patients reported a significantly shorter procedure time (166 versus 428 minutes, p<0.001), intensive care unit stay (40 versus 118 minutes, p<0.001), and length of hospital stay (6 versus 11 days, p<0.001), in the TMVIV group than SMVR group (Kamioka 2018).

A retrospective comparative case series of 1,788 patients with degenerated mitral bioprosthesis comparing TMVIV (n=384) with redo SMVR (n=1,404) reported that after propensity-score matching, length of hospital stay was shorter in patients who had TMVIV than those who had redo SMVR (5 days [range 2 to 11] versus 11 days [range 7 to 17], p<0.01; Osman 2020).

The retrospective comparative case series of 61 patients reported that TMVIV patients had shorter stays in the intensive care unit than those who had MIMVR (3±7 versus 5±4 days, p=0.02) and in the hospital (9±7 versus 14±7 days, p=0.03; Murzi 2017).

Safety summary

Death in-hospital

In the systematic review of 245 patients, mortality rates before discharge were 5% (9/172) and 7% (5/73) in the TMVIV and TMVIR groups respectively; 3% (5/172) and 7% (5/73) were cardiovascular related. No significant differences were found in death rate between patients who had different mode of failures (TMVIV MR 8% [3/39] versus MS 0% [0/24], p=0.404; TMVIR MR 7% [3/45] versus MS 0% [0/14] p>0.999) and those with different mitral valve access routes (TMVIV TA 3% [3/94] versus TS 7% [4/61], p=0.555; TMVIR, TA 10% [4/39] versus TS 3% [1/30], p=0.528) in both groups (Hu 2018).

The retrospective analysis of 1,079 patients reported that procedural mortality was less than 1% in the TMVIR group and 2% in the TMVIV group (p=0.10; Simonato 2020).

The retrospective analysis of 903 patients reported an overall all-cause in-hospital mortality rate of 8% (72/900) and was significantly lower in the TMVIV group than TMVIR and TVIMAC groups (TMVIV 6% [43/679], TMVIR 9% [11/123], and TVIMAC 18% [18/100]; p=0.004). The rate of cardiovascular

related deaths was 5% (43/900) and non-cardiovascular related deaths was 3% (29/900; Guerrero 2020).

The retrospective comparative case series of 1,788 patients reported that after propensity-score matching, in-hospital mortality was lower in patients who had TMVIV than those who had redo SMVR (4.8% versus 8.0%, p = 0.06; Osman 2020).

The retrospective comparative case series of 61 patients reported an in-hospital mortality rate of 5% (1/21) in the TMVIV group and 8% (3/40) in the MIMVR group (odds ratio [OR] 2.46; p=0.512). One patient in the TMVIV group had intraoperative mitral valve migration resulting in severe subaortic stenosis. The procedure was converted to open heart surgery for valve mispositioning, but the patient died of multiorgan failure (Murzi 2017).

Death within 30 days and 6 months

In the systematic review of 245 patients, at 30 days and 6 months follow up, the mortality rates in the TMVIV group were lower (7% [11/147] and 19% [16/85]) than the rates in the TMVIR group (9% [6/63] and 38%[10/26]) respectively (Hu 2018).

A meta-analysis of 17 studies with 248 patients (176 TMVIV and 72 TMVIR) showed a 30-day mortality rate of 5% for TMVIV (64/991, 95% CI 4.0% to 6.8%, I^2=0, p=0.685). Pooled analysis of 12 TMVIV studies (including 3 studies that reported TMVIR implantations) showed a mid-term (6-month to 5-year) mortality rate of 14% (88/587, 95% CI 9.0% to 18.5%; I^2=66%, p<0.001), and analysis of 6 transapical TMVIV studies showed non-significantly lower 30-day mortality when compared with predicted operative mortality (RR 0.58; 95% CI 0.24 to 1.45; p=0.25). The mean observed 30-day mortality rate was 6% and varied from 0 to 18% (Takagi 2018).

The retrospective analysis of 1,079 patients reported that 30-day mortality was 7% in the TMVIV group and 9% in the TMVIR group (p=0.29). Multivariable analysis shows that TMVIR was associated with substantially greater mortality than TMVIV procedures (Simonato 2020).

The retrospective analysis of 903 patients reported that 30-day overall all-cause mortality rate was 10% (n=79) and was statistically significantly lower in TMVIV and TMVIR groups than TVIMAC group (TMVIV 8% [47/584], TMVIR 8% [12/104], and TVIMAC 22% [n=20]; p=0.003). Overall, 6% (n=46) of these were cardiovascular related deaths and 4% (n=33) were non-cardiovascular related deaths (Guerrero 2020).

The retrospective analysis of 521 patients reported that all-cause 30-day mortality was lower in the TMVIV group followed by the TMVIR and TVIMAC groups (6% [20/322] versus 10% [14/141] versus 34% [20/58]; p<0.001; Yoon 2019).

The retrospective comparative case series of 121 patients reported that there was no statistically significant difference in mortality at 30 days between the 2 groups (TMVIV 3.2% versus SMVR 3.4%; p=1.00; Kamioka 2018).

In the case series of 50 patients the overall mortality rate at 30 days was 14%, with 1 intraprocedural death (da Costa 2020).

Death at 1 year

In the retrospective registry analysis of 521 patients, an overall mortality rate of 23% (117/521) was reported at a median follow up of 160 days (53 in the TMVIV group, 34 in the TMVIR group, and 30 in the TVIMAC group). The 1-year overall all-cause and cardiovascular mortality rates were 23% and 20% respectively. 1-year all-cause mortality was lower in the TMVIR group followed by TMVIV and TVIMAC groups (14% versus 31% versus 63%; TMVIV versus TMVIR; adjusted HR 1.99, 95% CI 1.27 to 3.12; p=0.003; TMVIV versus TVIMAC; adjusted HR 5.29, 95% CI 3.29 to 8.51; p<0.001; Yoon 2019).

The retrospective comparative case series of 121 patients reported that there was no statistically significant difference in mortality at 1 year between the 2 groups (TMVIV 11.3% versus SMVR 11.9%; p=0.92; Kamioka 2018).

The retrospective comparative case series of 61 patients reported late mortality in 4 patients in the TMVIV group as a result of pneumonia, endocarditis, lung cancer and stroke at 1, 8, 18 and 46 months postoperatively. In the MIMVR group, 5 patients died of cardiac failure (3 patients), sudden cardiac death and stroke at 2, 6, 25, 43 and 57 months postoperatively (Murzi 2017).

In a case series of 23 patients, an all-cause mortality rate of 10% (2/23) at a median follow up of 753 days was reported. Death was from respiratory failure in 1 patient (at 45 days) in whom the transatrial approach was converted to transapical implantation, and 1 was from an unknown cause (defined as cardiovascular according to Valve Academic Research Consortium-2) on day 135 (Cheung 2013, 2011).

Major adverse events

The retrospective comparative case series of 1,788 patients reported that after propensity-score matching, major adverse events were lower in patients who had

TMVIV than those who had redo SMVR (26% versus 44%, p<0.01; Osman 2020).

Left Ventricular Outflow Tract (LVOT) obstruction

In the systematic review of 245 patients, LVOT obstruction happened less frequently during the procedure in patients who had TMVIV procedures than those who had TMVIR procedures (TMVIV 0% [0/172] versus TMVIR 5% [4/73]; Hu 2018).

In the retrospective analysis of 1,079 patients, LVOT obstruction (defined as outflow mean gradient 10 mmHg or more or cardiogenic shock clinically related to a complication) during the procedure happened overall in 3% of patients and was less frequent in patients who had TMVIV (TMVIV 2%, TMVIR 6%, p=0.001; Simonato 2020).

In the retrospective analysis of 903 patients, LVOT obstruction during the procedure happened overall in 2% (21/902) of patients and was less frequent in patients who had TMVIV (TMVIV 1% [5/679], TMVIR 5% [6/123], and TVIMAC 10% [10/100], p<0.001; Guerrero 2020).

In the retrospective registry analysis of 521 patients, LVOT obstruction (defined as increment in mean gradient more than 10 mmHg from baseline) happened in 7% (37/521) of patients overall, with a statistically significantly lower rate after TMVIV than TMVIR and TVIMAC procedures (2% [7] versus 5% [7] versus 40% [23]; p<0.001; Yoon 2019).

Valve migration

In the systematic review of 245 patients, valve migration before discharge was reported in 2% (4/172) of patients who had TMVIV and rates at 30 days and 6 months increased to 5% (5/95) and 12% (7/60) respectively. No statistically significant differences were found between patients who had different mode of failures (MR 8% [3/39] versus MS 0% [0/24], p=0.404) and those with different mitral valve access routes (TA 1% [1/94] versus TS 2% [1/61] p>0.999). In the TMVIR group, valve migration was reported in 4% (3/73) of patients at discharge (3/73) and at 30 days (2/47) follow up. At 6 months it increased to 22% (2/9). No significant differences were found between patients who had different mode of failures (MR 10% [3/29] versus MS 0% [0/10], p=0.556) and those with different mitral valve access routes (TA 0% [0/39] versus TS 10% [3/30] p=0.155; Hu 2018).

In the retrospective analysis of 1,079 patients, statistically significantly fewer patients who had TMVIV reported valve migration/malposition/embolisation

during the procedure than those who had TMVIR (2% versus 7%; p=0.001; Simonato 2020).

In the retrospective analysis of 903 patients, valve migration during the procedure was reported in 4 patients (2 each in the TMVIV and TVIMAC groups, p=0.072). At 30 days follow up, valve migration was reported in another patient who had TMVIV (Guerrero 2020).

Valve embolisation

In the retrospective registry analysis of 903 patients, valve embolisations during the procedure and at 30 days follow up were less common in patients who had TMVIV, and the overall number of events were small (30 days: overall 0.8% [n=5], TMVIV 0.2% [n=1], TMVIR 4% [n=3], and TVIMAC 2% [n=1]; p=0.014; Guerrero 2020).

In the retrospective registry analysis of 521 patients, valve embolisations during the procedure were seen in 2% (9/521) of patients overall, and less frequently in patients who had TMVIV 0.9% (3/322) than those who had TMVIR 1% (2/141) and TVIMAC 7% (4/58; Yoon 2019).

Stroke

In the systematic review of 245 patients, strokes were reported before discharge in 2% (3/172) of patients who had TMVIV and rates at 30 days and 6 months increased to 3% (3/95) and 5% (3/56) respectively. No statistically significant differences were found in stroke rates between patients who had different mitral valve access routes (TA 2% [2/94] versus TS 2% [1/61]; p>0.999). In the TMVIR group, strokes were reported before discharge in 1% (1/73) of patients and rates at 30 days and 6 months increased to 2% (1/47) and 13% (1/8) respectively. No statistically significant differences were found in stroke rates between patients who had different mitral valve access routes (TA 3% (1/39) versus TS 0% (0/30); p>0.999; Hu 2018).

The retrospective registry analysis of 1,079 patients reported no significant difference in the rate of major strokes between the TMVIV and TMVIR groups (TMVIV 1%, TMVIR 0.5%; p=0.27; Simonato 2020).

In the retrospective analysis of 903 patients, ischemic stroke after the procedure and at 30 days follow up was significantly more common in patients who had TVIMAC, but the overall number of events were small (30 days: overall 2% [11], TMVIV 2% [7], TMVIR 0%, and TVIMAC 6% [4]; p=0.019; Guerrero 2020).

In the retrospective registry analysis of 521 patients, there were no statistically significant differences in strokes between the 3 groups (TMVIV 2% [7], TMVIR 0, TVIMAC 4% [2], p=0.10; Yoon, 2019).

The retrospective comparative case series of 61 patients reported that incidence of stroke was 5% (1/21) in the TMVIV group and 13% (5/40) in the MIMVR group (OR 0.887; p=0.935; Murzi 2017).

In the case series of 23 patients, major periprocedural stroke (complicated by nosocomial pneumonia and acute renal injury needing temporary renal replacement therapy) was reported in 1 patient. This patient had a prolonged intensive care stay and died on day 45 with respiratory failure, despite renal and neurological recovery (Cheung 2013, 2011).

Thrombosis

In the systematic review of 245 patients, thrombosis (on the ventricular aspect of the mitral bioprosthesis) was reported in 1 patient who had TMVIV before discharge (1/163) and rates at 30 days and 6 months increased to 3% (3/95) and 8% (5/60) respectively. One was because of leaflet thickening and reduced leaflet motion leading to device failure. No significant differences were found in thrombus rates between TMVIV patients who had different mode of failures (MR 3% (1/39) versus mitral stenosis 0% (0/24), p>0.999) and those with different mitral valve access routes (TA 1% (1/94) versus TS 0% (0/61) p>0.999; Hu 2018).

In the retrospective registry analysis of 903 patients, device thrombosis was reported in 1 patient in the TMVIV group (n=680) at 30 days follow up (Guerrero 2020).

In the retrospective registry analysis of 521 patients, clinical thrombosis during follow up was seen in 10 patients after TMVIV and 1 patient after TMVIR but none after TVIMAC (Yoon 2019).

Bleeding

In the systematic review of 245 patients, bleeding was reported in 9% (15/172) of TMVIV patients before discharge. These included 2 left ventricular apical perforations during the procedure and 13 access-site bleeding events after the procedure. No significant differences were found in bleeding rates between patients who had different mode of failures (MR 5% [2/39] versus MS 4% [1/24], p>0.999) and those with different mitral valve access routes (TA 9% (8/94) versus TS 8% (5/61) p=0.945; Hu 2018).

The retrospective registry analysis of 1,079 patients reported a statistically significant difference in the rate of major bleeding complications between the TMVIV and TMVIR groups (TMVIV 9%, TMVIR 5%; p=0.05; Simonato 2020).

The retrospective registry analysis of 903 patients reported no significant difference for major/life-threatening bleeding events during the procedure between the groups (overall 10% [n=89], TMVIV 10% [n=65], TMVIR 11% [n=14], TVIMAC 10% [n=10]; p=0.113; Guerrero 2020).

In the retrospective registry analysis of 521 patients, there were no significant differences in major or extensive bleeding events between the 3 groups (TMVIV 5% (n=14), TMVIR 4% (n=5) TMIVAC 2% (n=1), p=0.81). Life-threatening or fatal bleeding tended to be more frequent in the TMVIR group than the TMVIV and TVIMAC groups (TMVIR 7% [9] versus TMVIV 2% (7) versus TVIMAC 5% (2), p=0.07; Yoon 2019).

In the case series of 23 patients, major bleeding was reported in 26% (6/23) of patients (further details were not reported; Cheung 2013, 2011).

Pseudoaneurysm

In the systematic review of 245 patients, pseudoaneurysm rates in patients who had TMVIV at 30 days and 6 months were 2% (2/95) and 4% (2/55) respectively. In the TMVIR group 1% (1/73) reported pseudoaneurysm before discharge and 2% (1/47) at 30 days and 13% (1/8) at 6 months (Hu 2018).

Device failure

In the systematic review of 245 patients, device failure rates at 30 days and 6 months in the TMVIV group were 1% (1/95) and 6% (3/54) respectively. In the TMVIR group rates were 0% (0/47) and 14% (1/7) respectively (Hu 2018).

In the retrospective registry analysis of 903 patients, device failure was significantly lower in TMVIV and TMVIR groups and higher in TVIMAC group (overall 6% [53/902], TMVIV 5% [33/680], TMVIR 7% [8/123], and TVIMAC 12% [12/100]; p<0.001; Guerrero 2020).

Mitral valve reintervention

In the retrospective registry analysis of 903 patients, mitral valve reintervention during the procedure was significantly less common in patients who had TMVIV than those who had TMVIR and TVIMAC (overall 1% [11/902], TMVIV 3% [20/679], TMVIR 5% [6/123], TVIMAC 4% [4/100]; p=0.003). At 30 days follow

up, it was also significantly less common in patients who had TMVIV (overall, 1% [7], TMVIV 0.4 [2], TMVIR 1% [1], TVIMAC 6% [4]; p=0.002; Guerrero 2020).

Need for a second valve implantation

In the retrospective registry analysis of 1,079 patients, significantly fewer patients who had TMVIV needed a repeat transcatheter mitral valve replacement (MVR) than those who had TMVIR (3% versus 10%, p<0.001). The overall rate of repeat MVR at 4 years was 3% (18 events: 13 open heart surgery, 5 transcatheter), with a higher rate in patients who had TMVIR (6% versus 2% TMVIV; p<0.001). There was no significant difference in the 4-year rate of repeat MVR for patients with immediate post-procedural mean gradient of 5 mmHg or more (4% versus 2%; p=0.64), but the 4-year rate of repeat MVR was higher in patients with immediate post-procedural mean gradient of 10 mmHg or more (13% versus 2%; p<0.001). Both significant residual mitral stenosis (sub hazard ratio [SHR] 4.67; 95% CI 1.74 to 12.56; p=0.002) and significant residual mitral regurgitation (SHR 7.88; 95% CI 2.88 to 21.53; p<0.001) were associated with a need for repeat MVR (Simonato 2020).

In the retrospective registry analysis of 903 patients, significantly fewer patients who had TMVIV needed a second valve implantation during the procedure than those who had TMVIR and TVIMAC (overall 4% [33/902], TMVIV 2% [10/679], TMVIR 7% [9/123], and TVIMAC 14% [14/100]; p<0.001; Guerrero 2020).

In the retrospective registry analysis of 521 patients, second valve implantation was significantly less frequently done in TMVIV group than TMVIR and TVIMAC groups (3% [8] versus 12% [17] versus 5% [3] p<0.001; Yoon 2019).

In the case series of 23 patients, implantation of a second transapical TMVIV was needed (at 2 months, because of acute heart failure) in 1 patient. Echocardiography showed 4 to 5 mm atrial migration of the valve, which caused severe valvular regurgitation. A second transapical TMVIV implantation was done with no complications or valvular regurgitation (Cheung 2013, 2011).

Unplanned other cardiac surgery or intervention

In the retrospective case series of 903 patients, unplanned or other cardiac surgery or intervention during the procedure was significantly less common in the TMVIV group than the TMVIR and TVIMAC groups (overall 3% [n=27], TMVIV 2% [n=13], TMVIR 7% [n=9], TVIMAC 5% [n=5]; p=0.004; Guerrero 2020).

Acute kidney injury (AKI)

In the systematic review of 245 patients, AKI was reported in 5% (7/172) of patients who had TMVIV before discharge. No significant differences were found in AKI rates between patients who had different mode of failures (TMVIV MR 13% [5/39] versus MS 4% [1/24] p=0.487; TMVIR MR 3% [1/29] versus MS 10% [1/10], p=0.452) and those with different mitral valve access routes (TMVIV TA 9% [8/94] versus TS 3% [2/61]; p=0.337; TMVIR TA 8% [3/39] versus TS 0% [0/30]; p=0.327; Hu 2018).

In the retrospective registry analysis of 903 patients, need for dialysis was reported in 4% (33/903) of patients after the procedure. This was statistically significantly less common in patients who had TMVIV than those who had TMVIR and TVIMAC (TMVIV 3% [n=19], TMVIR 6% [n=7], TVIMAC 8% [n=7]; p=0.034). At 30 days follow up, there was no significant difference between the groups (overall 2% [n=12], TMVIV 2% [n=8], TMVIR 2% [n=2], TVIMAC 3% [n=2], p=0.767; Guerrero 2020).

The retrospective registry analysis of 1,079 patients reported no significant difference in the rate of AKI between the TMVIV and TMVIR groups (TMVIV 9%, TMVIR 13%; p=0.07; Simonato 2020).

In the retrospective registry analysis of 521 patients, stage 2 or 3 AKI happened less frequently in the TMVIV group than the TMVIR and TVIMAC groups (TMVIV 5% (n=14) versus TMVIR 10% (n=13) versus TVIMAC 15% (n=7), p=0.006; Yoon 2019).

In the case series of 23 patients, AKI (defined as stage 3 by VARC-2) was reported in 9% (2/23) of patients. One patient needed temporary renal replacement therapy (Cheung 2013, 2011).

New arrhythmia

In the systematic review of 245 patients, new arrhythmia was reported in 2% (3/172) of TMVIV patients and 3% (2/73) of TMVIR patients before discharge. No significant differences were found in arrhythmia rates between patients who had different mode of failures (TMVIV MR 5% [2/39] versus MS 0% [0/24], p=0.521; TMVIR 3% [1/29] versus 0% [0/10], p>0.999) and those with different mitral valve access routes (TMVIV TA 3% [3/94] versus TS 0% [0/61], p=0.417; TMVIR TA 3% (1/39) versus TS 0% (0/30), p >0.999) for both groups (Hu 2018).

Mitral regurgitation [MR] after procedure (including paravalvular leak and intervalvular regurgitation)

In the systematic review of 245 patients, MR (mild to moderate) was reported in 6% (8/145) of TMVIV patients before discharge. No significant differences were

found in MR rates between patients who had different mode of failures (MR 54% [2/53] versus MS 7% [2/30], p=0.954). In the TMVIR group, MR was reported in 12% (8/67) of patients before discharge and no significant differences were found in MR rates between patients who had different mode of failures (MR 5% [2/40] versus MS 13% [2/15], p=0.853; Hu 2018).

The retrospective registry analysis of 1,079 patients reported that significant residual mitral stenosis (defined as mean gradient 10 mmHg or more) happened in 8% of patients who had TMVIV and 12% of patients who had TMVIR (p=0.09) after the procedure and no significant association was found with survival at 4 years (66% versus 60%, p=0.89). Significant residual mitral regurgitation (defined as more than moderate) was more common in TMVIR patients (17% versus 3%; p<0.001) after the procedure and was associated with lower survival at 4 years (35% versus 62%; p=0.02). Correlates for residual mitral stenosis were smaller true internal diameter, younger age and larger body mass index. The only correlate for significant residual mitral regurgitation was TMVIR procedure (OR 7.90; 95% CI 4.01 to 15.56; p<0.001; Simonato 2020).

The retrospective registry analysis of 903 patients reported that most patients had residual mitral regurgitation grade of 1 or less after the procedure (overall 94% [848/903], TMVIV 96% [650/680], TMVIR 87% [107/123], TVIMAC 91% [91/100]). At 30 days follow up, residual mitral regurgitation grade 2 or more was significantly less common in patients who had TMVIV than those who had TMVIR and TVIMAC (overall 3% [15/458] TMVIV 2% [7/352], TMVIR 9% [5/54], and TVIMAC 6% [3/352]; p=0.010). Data about the type of residual mitral regurgitation (paravalvular or central) were unavailable. No significant differences were seen between the MR and MS groups but MS patients in the TMVIR group had higher mean transmitral gradient (TMVIR MR 4.2 mmHg [n=21] versus mitral stenosis 6.7 mmHg [n=15], p=0.002) (Guerrero 2020).

In the retrospective registry analysis of 521 patients, post-procedural MR (moderate or higher) was less frequently seen in the TMVIV group than TVIMAC and TMVIR groups (TMVIV 6% [n=18], TMVIR 18% [n=26], TVIMAC 14% [n=8]; p<0.001). At 30 days follow up, the rates of MR remained lower in the TMVIV group compared with TMVIR and TVIMAC groups (TMVIV 3% [n=10] versus TMVIR 13% [n=16] versus TVIMAC 13% [n=5]; p<0.001; Yoon 2019).

The retrospective comparative case series of 121 patients reported that the grade of mitral regurgitation (MR) were similar between the TMVIV group and the redo SMVR group (MR [moderate or greater] 4% versus 6%; p=1.00) at 30 days. At 1-year follow up, there was no difference in the grade of MR (4% [4/22] versus 4% [1/24], p=1.00; Kamioka 2018).

The retrospective comparative case series of 61 patients reported that some patients in the TMVIV group had mild paravalvular leakage (33% [7/21]), whereas no patients had mild paravalvular leakage in the MIMVR group (p<0.001; Murzi 2017).

Myocardial infarction

The retrospective registry analysis of 903 patients reported myocardial infarction in 4 patients after TMVIV implantation and in another 3 patients at 30 days follow up (Guerrero 2020).

Cardiac arrest

The retrospective registry analysis of 903 patients reported that cardiac arrest during the procedure was significantly lower in patients who had TMVIV (overall 5% [n=42], TMVIV 4% [n=26], TMVIR 5% [n=6], TVIMAC 10% [n=10]; p=0.022; Guerrero 2020).

Atrial fibrillation

The retrospective registry analysis of 903 patients reported that atrial fibrillation during the procedure was not significantly different between the 3 groups (overall 3% [n=23], TMVIV 2% [n=15], TMVIR 2% [n=3], TVIMAC 5% [n=5]; p=0.279; Guerrero 2020).

Vascular complications

The retrospective registry analysis of 1,079 patients reported that there were no significant differences in vascular complication rates between the TMVIV and TMVIR groups (TMVIV 2% versus TMVIR 6%, p=0.06; Simonato 2020).

The retrospective registry analysis of 903 patients reported that there were no significant differences in vascular complication rates between the TMVIV, TMVIR and TVIMAC groups (overall 3% [n=30], TMVIV 3% [n=20], TMVIR 5% [n=6], and TVIMAC 4% [n=4]; p=0.518; Guerrero 2020).

In the retrospective registry analysis of 521 patients, major vascular complications happened less frequently in the TMVIV group than the TMVIR and TVIMAC groups (2% [n=5] versus 4% [n=5] versus 8% [n=4]; p=0.019) at 30 days follow up (Yoon 2019).

Conversion to surgery (including unplanned vascular surgery/interventions)

The retrospective registry analysis of 903 patients reported that there were no significant differences between the groups for rates of conversion to surgery (overall 2% [n=14], TMVIV 1% [n=9], TMVIR 2% [n=3], TVIMAC 2% [n=2]; p=0.579) and unplanned vascular surgery or interventions (overall 3% [n=27], TMVIV 2% [n=13], TMVIR 2% [n=3], TVIMAC 2% [n=2]; p=0.920; Guerrero 2020).

In the retrospective registry analysis of 521 patients, conversion to surgery during the procedure was seen in 2% (12/521) of patients overall, and less frequently after TMVIV 1% (3/322) than TMVIR 3% (4/141) and TVIMAC 9% (5/58) groups; p=0.004 (Yoon 2019).

Cardiac perforations

The retrospective registry analysis of 903 patients reported that there were no significant differences in cardiac perforation rates between the TMVIV, TMVIR and TVIMAC groups (overall 2% [n=19], TMVIV 2% [n=13], TMVIR 2% [n=3], TVIMAC 3% [n=3]; p=0.798; Guerrero 2020).

Re-interventions

In the retrospective registry analysis of 521 patients, paravalvular leak closure during the procedure was more frequently done in the TMVIR group than the TMVIV and TVIMAC groups (8% [n=11] versus 2% [n=7] versus 0%; p=0.006), whereas alcohol septal ablation was more frequently done in the TVIMAC group than TMVIV and TMVIR groups (12% [n=7] versus 1% [n=2] versus 1% [n=1]; p<0.001). There were no significant differences in atrial septal defect closure (p=0.38) and surgical/transcatheter mitral valve replacement (p=0.98) between the 3 groups (Yoon 2019).

Readmissions

The retrospective comparative case series of 1,788 patients reported that after propensity-score matching, rate of readmissions was similar between the TMVIV and SMVR groups (15% versus 15%, p=0.925; Osman 2020).

Patient prosthesis mismatch

The retrospective registry analysis of 1,079 patients reported no significant difference in the rate of severe patient prosthesis mismatch between the TMVIV and TMVIR groups (TMVIV 24%, TMVIR 27%; p=0.54) (Simonato 2020).

Other complications

Haemothorax (drained with a thoracostomy tube) was reported in 1 patient in the case series of 23 patients. Atrial clot (detected at 6-month follow up echocardiogram) was reported in in the same study. The patient was asymptomatic with no embolic events but was treated with systemic anticoagulation. Permanent pacemaker implantation (on day 3 for pre-existing atrioventricular conduction disturbance) was also needed in 1 patient (Cheung 2013, 2011).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, we received no questionnaires.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. The following databases were searched, covering the period from their start to 03-08-2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria shown in the following table were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with failed surgically implanted mitral valve bioprosthesis.
Intervention/test	Transapical transcatheter mitral valve-in-valve implantation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 4808 patients (2674 patients with TMVIV, 631 patients with TMVIR, and 1503 patients with redo SMVR) from 2 systematic reviews[1-2], 3 retrospective registry analyses[3-5], 3 retrospective comparative studies[6-8] and 2 case series[9-10]. There might be an overlap of studies included in the systematic reviews[1-2]. The case series[9-10] and comparative studies[6, 8] are included in the systematic reviews.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis

Evidence on TMVIV implantations presented in studies below[1-6] included data on both transapical and transseptal access routes. Approximately, 60% of the procedures were done using the transapical access route and 40% were done using the percutaneous transeptal access route. Data is presented as per access routes where subgroup analyses are available.

Study 1 Hu J (2018)

Study details

Study type	Systematic review and meta-analysis
Country	China
Search period	Search period from 2000 to 2018; databases searched: PubMed, Web of Science
Study population and number	**n=245 patients** (from 101 studies) having transcatheter mitral valve-in-valve (TMVIV) and valve-in-ring implantation (TMVIR) for degenerated mitral bioprostheses and failed annuloplasty rings. **TMVIV (n=172 from 66 studies); TMVIR (n=73 from 35 studies)** Failure mode, %: TMVIV mitral regurgitation 49 (71/144), mitral stenosis 32 (46/144), mixed 19 (27/144) TMVIR mitral regurgitation 68 (45/66), mitral stenosis 24 (16/66), mixed 7.6 (5/66) Logistic EuroSCORE (%): overall 19.1 ± 12.8 (n=91); TMVIV 36.4 ± 17.1 (n=69); TMVIR 37.8 ± 21.4 (n=22) STS score (%): overall 15.6 ± 13.5 (n=130); TMVIV 16.8 ± 15.2 (n=86); TMVIR 13.4 ± 9.0 (n=44) NYHA class > III (%): overall 98.2 (165/168); TMVIV 97.3 (108/111) and TMVIR 100.0 (57/57) Mitral regurgitation severe or grade 3, %: TMVIV 63.3 (76/120); TMVIR 80.3 (53/66) LVEF (%): overall 46.7 (n=106); TMVIV; 51.2 (n=73); TMVIR 36.7 (n=33)
Age and sex	Mean age (years): overall 73; TMVIV 74; TMVIR 70. Gender (male), %: overall 50.6 (84/166); TMVIV 46.5 (53/114); TMVIR 59.6 (31/52)
Study selection criteria	Inclusion criteria: patients who had either a TMVIV or TMVIR implantation and reported data on baseline characteristics and outcomes.

	Exclusion criteria: non-English studies; animal studies; studies with no data on TMVI implantation, lack of details regarding postoperative outcomes; duplicate studies; TMVIV or TMVIR for native mitral valve; insertion of a TMVIV or TMVIR during a sternotomy under direct vision; and conference abstracts.
Technique	Transcatheter mitral valve-in-valve (TMVIV=172) and valve-in-ring (TMVIR=73) implantation. **Access route used:** transapical access 55% (127/245); transseptal access via transfemoral or transjugular venous route 37.7% (91/245); direct transatrial access via a right anterior thoracotomy in 2 patients. Type of valves used: Edwards SAPIEN XT (n = 120), SAPIEN (n = 47), SAPIEN 3 (n = 26), Medtronic melody (n = 18), Tiara (n = 4), Lotus (n = 3, Boston Scientific), Tendyne (n = 1), and Direct Flow Medical (n = 9).
Follow up	6 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: long term follow-up data were limited; only 40% patients completed 6 months follow up and few studies reported 1-year follow up.

Study design issues: study was done in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Comprehensive systematic search was done, 2 reviewers extracted data using predefined criteria and forms. Survival curves were estimated using Kaplan–Meier method. The results are stratified according to the mitral valve failure mode and access route.

Study population issues: some patients had previous history of heart surgery, comorbidities and other valve dysfunctions. Patients who had TMVIV via a transapical access had a higher incidence of concomitant aortic and tricuspid valve dysfunction than those who had via a transseptal access (56% versus 16.7%, p=0.001). More patients in the transapical group had previous surgeries (58% versus 34.6%, p=0.035).

Other issues: primary studies included in this systematic review might overlap with those included in study 2.

Key efficacy findings

Number of patients analysed: 245 (172 TMVIV and 73 TMVIR)

In-hospital implantation and clinical outcomes

Clinical outcome	All patients % (n=245)	TMVIV % (n=172)	TMVIR % (n=73)
Technical success^, %	93.5 (229/245)	97.1 (167/172)	84.9 (62/73) p=0.001
Technical failures %	6.5 (18/245)	2.9 (5/172) *	15.1 (13/73)
Postprocedural mean trans-mitral gradient, (mmHg, mean ± SD)	5.1 ± 2.5 (n=140)	5.1 ± 2.5 (n=96)	5.1 ± 2.5 (n=44)
NYHA (at latest follow-up) ≤2, %	94.0 (109/116)	92.0 (69/75)	97.6 (40/41)

^ defined according to the Mitral Valve Academic Research Consortium (MVARC) criteria (device success and no occurrence of in-hospital or 30-day death).

*2 were because of technical operative error, and 3 were because of prosthesis migration: 2 into the left atrium and 1 into the left ventricle.

Subgroup analysis (failure mode)

	TMVIV failure mode			TMVIR failure mode		
Clinical outcome	Mitral Regurgitation	Mitral Stenosis	P value	Mitral Regurgitation	Mitral Stenosis	P value
Technical success^, %	94.3 (50/53)	100 (35/35)	0.405	86.0 (37/43)	92.9 (13/14)	0.837
Postprocedural mean transmitral gradient, (mmHg, mean ± SD)	5.6 ± 2.7 (n=45)	5.0 ± 3.2 (n=28)	0.378	4.2 ± 1.9 (n=21)	6.7 ± 2.4 (n=15)	0.002
NYHA (at latest follow-up) ≤2, %	94.3 (33/35)	100.0 (14/14)	>0.999	94.7 (18/19)	100.0 (9/9)	>0.999

Subgroup analysis (access route)

	TMVIV access route			TMVIR access route		
Clinical outcome	Transapical	Transseptal	P value	Transapical	Transseptal	P value
Technical success^, %	98.9 (93/94)	95.1 (58/61)	0.337	89.7 (35/39)	86.7 (26/30)	0.427
Postprocedural mean transmitral gradient, (mmHg, mean ± SD)	5.1 ± 3.1 (n=39)	5.4 ± 2.5 (n=43)	0.652	4.3 ± 2.3 (n=19)	5.9 ± 2.6 (n=21)	0.071
NYHA (at latest follow-up) ≤2, %	93.9 (46/49)	100.0 (12/12)	>0.999	100.0 (18/18)	93.3 (14/15)	0.455

Subgroup analysis (overall survival for patients with different failure modes and access routes)

TMVIV implantation-No significant differences in overall survival curves were seen for patients with different failure modes (mitral regurgitation or mitral stenosis, p=0.347) and different access routes (transapical or transeptal, p=0.450).

TMVIR implantation - No significant differences in overall survival curves were seen for patients with different failure modes (mitral regurgitation or mitral stenosis, p=0.958) and different access routes (transapical or transeptal, p=0.361).

Clinical outcomes before and after the procedure

	Pre-procedure	Post-procedure	P value
Mean transmitral gradient (mmHg, mean ± SD)			
All patients	12.1 ± 5.9 (n=155)	5.1 ± 2.5 (n=140)	<0.001
TMVIV	12.8 ± 5.9 (n=121)	5.1 ± 2.5 (n=96)	<0.001
TMVIR	9.5 ± 5.2 (n=34)	5.1 ± 2.5 (n=44)	<0.001
NYHA ≥ 3, %			
All patients	98.2 (165/168)	6.2 (7/113)	<0.001
TMVIV	97.3 (108/111)	8.1 (6/74)	<0.001
TMVIR	100.0 (57/57)	3.6 (1/39)	<0.001

Key safety findings

Adverse events

In-hospital safety outcomes

Patient-reported outcome	All patients % (n)	TMVIV % (n)	TMVIR % (n)
Death^^, %	5.7 (14/245)	5.2 (9/172)	6.8 (5/73)
Cardiovascular related deaths %	NR	2.9 (5/172)	6.8 (5/73)
Valve migration %	2.9 (7/245)	2.3 (4/172)	4.1 (3/73)
Left ventricular outflow tract (LVOT) obstruction %	1.6 (4/245)	0.0 (0/172)	5.5 (4/73)
Postprocedural mitral regurgitation^ %			
Trace	69.3 (147/212)	73.8 (107/145)	59.7 (40/67)
Mild or grade 1	23.1 (49/212)	20.7 (30/145)	28.3 (19/67)
>mild	7.6 (16/212)	5.5 (8/145)	12.0 (8/67)
Access site and vascular complications %			
Bleeding	6.1 (15/245)	8.7 (15/172) *	0.0 (0/73)
Thrombus**	0.4 (1/236)	0.6 (1/163)	0.0 (0/73)
Pseudoaneurysm	0.4 (1/236)	0.0 (0/163)	1.4 (1/73)
Stroke %	1.6 (4/245)	1.7 (3/172)	1.4 (1/73)
Myocardial infarction %	0.0 (0/245)	0.0 (0/172)	0.0 (0/73)
New arrhythmia %	2.0 (5/245)	1.7 (3/172)	2.7 (2/73)
Acute kidney injury %	4.5 (11/245)	4.1 (7/172)	5.5 (4/73)

^^includes 2 intraoperative deaths (left ventricular apical perforation) and 12 postoperative deaths.

^Including paravalvular leak and intervalvular regurgitation.

*including 2 left ventricular apical perforations during the procedure and 13 access site bleedings after the procedure.

** one the ventricular aspect of the mitral valve prosthesis, one because of device failure: leaflet thickening and reduced leaflet motion.

Adverse events at follow-up period

	All patients		TMVIV		TMVIR	
	30 days	6 months	30 days	6 months	30 days	6 months
Death %	8.1 (17/210)	23.4 (26/111)	7.5 (11/147)	18.8 (16/85)	9.5 (6/63)	38.5 (10/26)
Pseudoaneurysm %	2.1 (3/142)	4.8 (3/63)	2.1 (2/95)	3.6 (2/55)	2.1 (1/47)	12.5 (1/8)
Stroke %	2.8 (4/142)	6.3 (4/64)	3.2 (3/95)	5.4 (3/56)	2.1 (1/47)	12.5 (1/8)
Myocardial infarction %	0.0 (0/142)	0.0 (0/60)	0.0 (0/95)	0.0 (0/53)	0.0 (0/47)	0.0 (0/7)
Thrombus %	2.1 (3/142)	7.5 (5/67)	3.2 (3/95)	8.3 (5/60)	0.0 (0/47)	0.0 (0/7)

IP overview: Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis

Device migration %	4.9 (7/142)	13.0 (9/69)	5.3 (5/95)	11.7 (7/60)	4.3 (2/47)	22.2 (2/9)
Device failure %	0.7 (1/142)	6.6 (4/61)	1.1 (1/95)	5.6 (3/54)	0.0 (0/47)	14.3 (1/7)
Need for implantable cardiac defibrillator %	1.4 (2/142)	3.2 (2/62)	1.1 (1/95)	1.9 (1/54)	2.1 (1/47)	12.5 (1/8)
Atrial septal defect closure %	6.3 (9/142)	13.0 (9/69)	7.4 (7/95)	11.7 (7/60)	4.3 (2/47)	22.2 (2/9)

^one because of device failure, leaflet thickening and reduced leaflet motion.

Subgroup analysis (in-hospital outcomes- failure mode)

	TMVIV failure mode			**TMVIR failure mode**		
Clinical outcome	**Mitral Regurgitation**	**Mitral Stenosis**	**P value**	**Mitral Regurgitation**	**Mitral Stenosis**	**P value**
Death %	7.7 (3/39)	0.0 (0/24)	0.404	6.7 (3/45)	0 (0/14)	>0.999
Valve migration %	7.7 (3/39)	0.0 (0/24)	0.404	10.3 (3/29)	0 (0/10)	0.556
LVOT obstruction %	0 (0/39)	0 (0/24)	-	6.9 (2/29)	10 (1/10)	>0.999
Postprocedural mitral regurgitation^ %						
None/ Trace	84.9 (45/53)	77.7 (23/30)	0.349	70 (28/40)	66.7 (10/15)	>0.999
Mild or grade 1	11.3 (6/53)	16.7 (5/30)	0.724	25 (10/40)	20 (3/15)	0.974
>mild	3.8 (2/53)	6.8 (2/30)	0.954	5.0 (2/40)	13.3 (2/15)	0.853
Access site and vascular complications %						
Bleeding	5.1 (2/39)	4.2 (1/24)	>0.999	0 (0/29)	0 (0/14)	-
Thrombus	2.6 (1/39)	0.0 (0/24)	>0.999	0 (0/29)	0 (0/14)	-
Pseudoaneurysm	0 (0/39)	0 (0/24)	-	0 (0/29)	0 (0/14)	-
Stroke %	0 (0/39)	0 (0/24)	-	0 (0/29)	0 (0/14)	-
Myocardial infarction %	0 (0/39)	0 (0/24)	-	0 (0/29)	0 (0/14)	-
New arrhythmia %	5.1 (2/39)	0 (0/24)	0.521	3.4 (1/29)	0 (0/10)	>0.999
Acute kidney injury %	12.8 (5/39)	4.2 (1/24)	0.487	3.4 (1/29)	10 (1/10)	0.452

^Including paravalvular leak and intervalvular regurgitation.

Subgroup analysis- in-hospital outcomes (access route)

	TMVIV access route			TMVIR access route		
Clinical outcome	**Transapical**	**Transeptal**	**P value**	**Transapical**	**Transseptal**	**P value**
Death %	3.2 (3/94)	6.6 (4/61)	0.555	10.3 (4/39)	3.3 (1/30)	0.528
Valve migration %	1.1 (1/94)	1.6 (1/61)	>0.999	0 (0/39)	10 (3/30)	0.155
LVOTO %	0.0 (0/94)	0.0 (0/61)		5.1 (2/39)	6.7 (2/30)	>0.999
Postprocedural mitral regurgitation^ %						
None/ Trace	98.9 (92/93)	100.0 (61/61)	>0.999	63.2 (24/38)	44 (11/25)	0.134
Mild or grade 1	1.1 (1/93)	0.0 (0/61)	>0.999	23.7 (9/38)	44 (11/25)	0.090
>mild	0.0 (0/93)	0.0 (0/61)		13.2 (5/38)	12 (3/25)	>0.999
Access site and vascular complications %						
Bleeding	8.5 (8/94)	8.2 (5/61)	0.945	0 (0/39)	0 (0/30)	
Thrombus	1.1 (1/94)	0.0 (0/61)	>0.999	0 (0/39)	0 (0/30)	
Pseudoaneurysm	0.0 (0/94)	0.0 (0/61)		0 (0/39)	3.3 (1/30)	0.435
Stroke %	2.1 (2/94)	1.6 (1/61)	>0.999	2.6 (1/39)	0 (0/30)	>0.999
Myocardial infarction %	0.0 (0/94)	0.0 (0/61)		0 (0/39)	0 (0/30)	
New arrhythmia %	3.2 (3/94)	0.0 (0/61)	0.417	2.6 (1/39)	0 (0/30)	>0.999
Acute kidney injury %	8.5 (8/94)	3.3 (2/61)	0.337	7.7 (3/39)	0 (0/30)	0.327

^Including paravalvular leak and intervalvular regurgitation.

Study 2 Takagi H (2018)

Study details

Study type	Meta-analysis
Country	Japan
Study search period	Search period: from inception to 2018; databases searched: Medline, Embase using PubMed and Ovid search engines. Manual searching of references in included studies, and a search of reviews and commentaries were also done.
Study population and number	**N=17 studies (with 1017 patients)** with transcatheter mitral valve in valve implantation [TMVIV] for deteriorated bioprosthetic valves and/or valve-in-ring [TMVIR] for failed annuloplasty rings. (11 studies on TMVIV [2 of these compared TMVIV with redo mitral surgery], 1 study on TMVIR, 2 studies combined TMVIV and TMVIR, 3 studies assessed TMVIV and TMVIR separately).
Age	Median age was 75 years; 59.2% female
Patient selection criteria	Studies with more than 10 patients with a deteriorated mitral bioprosthetic valve or a failed mitral annuloplasty ring who had TMVIV or TMVIR; reporting at least 30-day all-cause mortality were included. Duplicate or multicentre publications were excluded.
Technique	Transcatheter mitral valve-in- valve implantation (TMVIV) for deteriorated bioprosthetic valves and/or transcatheter mitral valve-in-ring [TMVIR] for failed annuloplasty rings. Access route: transapical access (7 studies); transeptal access (2 studies TMVIV and 1 study TMVIR; and both (in 7 studies). Transapical approach used in 40.4% patients, transeptal approach in 55.5% patients.
Follow-up	Varied (1 to 5 years)
Conflict of interest/source of funding	None

Analysis

Follow-up issues: varied follow up in studies.

Study design issues: comprehensive search was done; most studies included were on TMVIV implantations. Study compared observed 30-day mortality with predicted operative mortality. Risk ratios (RR) were generated using observed 30-day mortality and predictive operative mortality (STS-PROM) from each study. These were combined using the inverse variance-weighted average of logarithmic RRs in the random-effects model. Meta-analyses of 30-day and late mortality rates were done. Sensitivity analyses, meta-regression analyses were done, and publication bias was assessed.

Study population issues: study also included 73 patients with TMVIR implantations in the meta-analysis.

Other issues: primary studies included in this systematic review might overlap with those included in study 1.

Key efficacy findings

- Number of patients analysed: 248 (176 TMVIV and 72 TMVIR)

Key safety findings

Pooled analysis of 30-day mortality rates

Pooled analyses of 17 TMVIV studies (including 3 studies that reported TMVIR implantations) showed a 30-day mortality rate of 5.4% (64/991, 95% CI, 4.0 to 6.8%, I^2=0, p=0.685).

Pooled analysis of mid term/late mortality rates
Pooled analyses of 12 TMVIV studies (including 3 studies that reported TMVIR implantations) showed a mid-term (6-month to 5-year) mortality rate of 13.7% (88/587, 95% CI, 9.0 to 18.5%; I^2=66%, p<0.001).

Meta-analysis of risk ratios for observed 30-day mortality versus predicted operative mortality
Pooled analysis of 13 studies showed that observed 30-day mortality was significantly lower than predicted operative mortality (RR, 0.67; 95% CI, 0.49 to 0.91; p = 0.01; I^2 = 0%).

Meta-analysis of risk ratios for observed 30-day mortality versus predicted operative mortality in transapical TMVIV implantations
Pooled analysis of 6 TA-TMVIV studies (including a total of 111 patients) showed that observed 30-day mortality was non significantly lower than predicted operative mortality (RR, 0.58; 95% CI, 0.24 to 1.45; p = 0.25).

The mean observed 30-day mortality rate was 6% and varied from 0 to 18%.

Study 3 Simonato M (2020)

Study details

Study type	Retrospective registry analysis (Valve-in-Valve International Data [VIVID] registry)
Country	Worldwide (from 90 centres)
Recruitment period	2006 to 2020
Study population and number	**N=1,079 high risk patients with recurrent mitral valve failure after previous surgical valve repair or replacement.** **(857 TMVIV versus 222 TMVIR)**

	Median STS-PROM score overall 8.6% (5.4 to 14.1); TMVIR 9.0 [5.6 to 14.3] versus TMVIV 7.4 [4.6 to 13.0]; p=0.006 LVEF %: overall 53.2 ± 12.7, TMVIV 55.2 ± 11.3 versus TMVIR45.1 ± 14.8; p< 0.001 NYHA class 3/4: overall 96%, TMVIV 89.5% versus TMVIR 94.9%, p=0.02 Time to index surgery (years): overall 9.2 [5.8 to 12.8], TMVIV 9.8 [6.5 to 13.1] versus TMVIR 6.8 [3.2 to 10.4], p< 0.001 Mechanism of bioprosthetic valve failure: (defined according to European Association of Echocardiography and American Society of Echocardiography criteria) mitral regurgitation [MR grade 3-4]: overall 15.4%, TMVIV 10.2%, TMVIR 35.6% mitral stenosis [MS] overall 27.6%, TMVIV 30.7%, TMVIR 15.3% mixed (moderate MR and MS): overall 57.1%, TMVIV 59.1%, TMVIR 49.1%
Age	Overall mean age (years) 73.5; TMVIV 74.1 versus TMVIR 71.2; p= 0.002. Overall, 40.8% male; TMVIV 38.2% versus TMVIR 50.9%, p= 0.001
Patient selection criteria	High risk surgical patients who had transcatheter mitral VIV and VIR procedures and included in the registry.
Technique	**TMVIV n=857** **TMVIR-n=222** **General anaesthesia:** in overall 97.4% patients. **Devices used:** multiple types (overall Sapien 41.8% (n=446), other devices 58.2%) **Device size, mm: o**verall 27.1, TMVIV 27.1, TMVIR 26.7, p=0.01 **Access: (p=0.002)** Transapical-overall 61.6%, TMVIV 64.4%, TMVIR 50.7% Transseptal- overall 36.9%, TMVIV 34.5%, TMVIR 46.4% Right thoracotomy overall 1.0%, 0.7% TMVIV, TMVIR 1.9% Other- overall 0.5%; TMVIV 0.4%; TMVIR 0.9% All included patients were discharged on antiplatelets or anti-coagulants (96.2%) after the procedure. anticoagulation for TMVIV and TMVIR was not significantly different (70.8% vs. 76.6%; p = 0.15).
Follow-up	Median clinical follow-up 492 days [IQR 76 – 996 days]. TMVIV group (519 days [IQR 95.5 to 1007 days] versus TMVIR group 426 days [IQR 40.8 to 895 days], p = 0.11). Median echocardiographic follow-up for patients that survived 1 year (n=466): 772.5 days [IQR 510 to 1211.75 days].
Conflict of interest/source of funding	This study was funded by the Institute of Valvular Research. Some authors have worked as consultants, proctors and received research or educational or travel grants, personal or speaker or training fees, honorarium from device companies.

Analysis

Follow-up issues: long follow-up period but large number of missing follow-up data. Echocardiographic follow up for 30% of patients alive at 1 year is missing from longer follow up.

Study design issues: large retrospective observational registry analysis, data were collected through a centralised form and inconsistencies were resolved through discussion with investigators. Primary end point was patient survival; secondary end points were significant residual mitral stenosis, mitral regurgitation and rate of repeat mitral valve replacement. Clinical endpoints are reported according to the Mitral Valve Academic Research Consortium (MVARC) definitions. Study included real world data from large number of centres with a large sample size. Logistic regression was used to determine independent correlates of significant residual mitral stenosis and significant residual mitral regurgitation. Cox regression was done to establish independent correlates of survival. A Fine and Gray cause specific sub distribution hazards model was used to determine the independent correlates of repeat TMVR.

Study population issues: all patients had multiple comorbidities.

Other issues: Transapical access was utilized in many cases. Authors state that 'there was a significant increase in the proportion of transseptal access over years (15.6% in 2006 to 2013, 30.7% in 2014 to 2016 and 62.7% in 2017 to 2020; $p < 0.001$). Authors also state that 'there were significant shifts toward treating lower risk patients and increasingly used transseptal access over time'. They further state that transapical access may add to procedural morbidity and is less commonly used nowadays.

Key efficacy findings

- Number of patients analysed: 1,079 (857 TMVIV versus 222 TMVIR)

Implantation and procedure outcomes

	Overall % (n=1079)	TMVIV % (n=857)	TMVIR % (n=222)	P value
Technical success^	91.1	93.5	82.0	<0.001
Device success*	39.4	41.3	32.0	0.01
Modified device success**	79.7	84.0	63.1	<0.001
Device success without haemodynamic criteria^^	90.3	92.5	81.5	<0.001

^technical success is exit from Cath lab by MVARC criteria (absence of procedural mortality; successful access, delivery, and retrieval of the device delivery system; successful deployment of the first intended device; and freedom from emergency surgery or re-intervention related to the device or access procedure).

*Device success: absence of procedural mortality or stroke, and proper placement and positioning of the device, and freedom from unplanned surgical or interventional procedures related to the device or access procedure, and continued intended safety and performance of the device, including no evidence of structural or functional failure, no specific device-related technical failure issues and complications and reduction of mitral regurgitation to either optimal or acceptable levels without significant mitral stenosis (that is, post-procedure

effective regurgitant orifice area is ≥ 1.5 cm2 with a trans-mitral gradient <5 mmHg), and with no greater than mild (1+) paravalvular MR (and without associated hemolysis).

**Considering trans-mitral gradient ≥10 mmHg as a cut-off.

^^Considering only the components of device success not related to hemodynamics, that is procedural death, malposition/embolization/migration, second transcatheter heart valve, left ventricular outflow tract obstruction and stroke.

Survival rate (Kaplan–Meier survival estimates)

	Overall (n=1079)	TMVIV (n=857)	TMVIR (n=222)	P value
1 year		86.2%	76.8%	0.004
4 years		62.5%	49.7	0.002

Patients at high risk for repeat open heart surgery (STS score ≥ 8%) also had significantly worse survival at 4 years (TMVIV 66.8% versus 54.1%, p<0.001).

Echocardiographic outcomes (at median 772.5 days, IQR 510 to 1,211.75 days)

	Overall (n=1079)	TMVIV (n=857)	TMVIR (n=222)	P value
Left ventricular ejection fraction %				
Baseline	53.2 ± 12.7	55.2 ± 11.3	45.1 ± 14.8	<0.001
Post procedure	52.1 ± 12.8	53.8 ± 11.4	45.2 ± 15.4	<0.001
Mitral valve gradient, mm Hg (mean ±SD)				
Baseline	10.7 ± 5.9	11.4 ± 5.9 (n=824)	7.8 ± 5.0 (n=196)	<0.001
Post procedure	5.7 ± 2.8	5.6 ± 2.7 (n=733) (p<0.001)	6.0 ± 2.8 (n=191) (p<0.001)	0.08
>1 year	N=446	6.7±2.7 (n=343) (p<0.001)	6.5±3.1 (n=77) (p=0.20)	
Mitral valve area, cm^2				
Baseline	1.50 ± 0.91	1.41 ± 0.83 (n=520)	1.87 ± 1.09 (n=125)	<0.001
Post procedure	2.04 ± 0.74	2.01 ± 0.74 (n=390) (p<0.001)	2.13 ± 0.74 (n=101) (p=0.03)	0.17
>1 year		2.00 ±0.78 (n=137) (p=0.85)	1.99±0.90 (n=28) (p=0.40)	

Patients with TMVIV implantation with small valves (true ID ≤ 23 mm) did not have a significant increase in their gradients in 1-year follow up.

Mitral regurgitation (MR)

	Overall % (n=1,070)	TMVIV % (n=857)	TMVIR % (n=222)	P value
Baseline				**<0.001**
None/trace	13.5	15.2	6.8	
Mild	13.7	15.1	8.2	
Moderate	12.5	12.6	12.3	
Moderate to severe	17.4	15.3	25.0	
Severe	43.0	41.7	47.7	
MR post procedure				**<0.001**
None/trace	71.7	77.0	50.7	
Mild	22.5	19.9	32.7	
Moderate	5.0	2.9	12.8	
Moderate to severe	0.5	0.0	2.4	
Severe	0.4	0.1	1.4	

There were significant post-procedure decreases in MR severity after both TMVIV and TMVIR procedures. The distribution of MR severity remained stable during 1-year follow up after TMVIR procedures (p=0.48) but the proportion of ≥ moderate MR increased at 1year follow up in the TMVIV group (p=0.02).

Key safety findings

Complications and adverse events

	Overall % (n=1079)	TMVIV % (n=857)	TMVIR % (n=222)	P value
Procedural complications				
Left ventricular outflow tract obstruction (outflow mean gradient ≥ 10mmHg or cardiogenic shock clinically related to a complication)	2.6	1.8	5.9	0.001
Malposition*/embolization/migration	3.3	2.4	7.0	0.001
Second transcatheter mitral valve implantation	4.3	2.8	10.1	<0.001
Procedural mortality	1.8	2.1	0.5	0.10
Vascular complications	5.0	5.7	1.9	0.06
Major	2.7	3.2	0.5	
Minor	2.3	2.5	1.4	
Major bleeding complications	8.0	8.8	4.7	0.05

Significant residual mitral stenosis (post-procedure mean gradient ≥10 mmHg)	8.9	8.2	12.0	0.09
Residual mitral stenosis (immediate post-procedure >5mmHg)	61.4	59.9	67.5	0.05
Significant residual mitral regurgitation (regurgitation ≥ moderate) ^^	5.8	3.1	16.6	<0.001
Acute kidney injury	9.6	8.8	13.0	0.07
Major stroke	1.2	1.4	0.5	0.27
30-day mortality	7.0	6.5	8.5	0.29
Severe prosthesis-patient mismatch (PPM)	24.5	23.8	26.9	0.54
Repeat MVR at 4 years	2.7% (18 events, 13 open, 5 transcatheter)	1.9	5.9	<0.001
4-year repeat MVR for patients with immediate post-procedural mean gradient ≥ 5 mmHg		1.6	3.8	0.64
4-year repeat MVR for patients with immediate post-procedural mean gradient ≥10 mmHg		2	13.4	<0.001

*defined as inadequate final position of the transcatheter heart valve for any cause.

^ defined as indexed effective orifice area (EOA) ≤ 0.9 cm2/m2 for patients with body mass index (BMI) < 30 kg/m2 and indexed EOA ≤ 0.75 cm2/m2 for those with BMI ≥ 30 kg/m2

^^ significant residual MR was associated with lower survival at 4 years (35.1% vs. 61.6% no residual MR; p = 0.02). No association was found for significant residual MS (66.1% vs. 60.5% immediate post-procedural mean gradient <10 mmHg; p = 0.89).

Multivariate analysis

In a Cox regression model, TMVIR as compared with TMVIV was independently associated with mortality (HR 1.52; 95% CI 1.03 to 2.25; p = 0.04).

Correlates for residual mitral stenosis were smaller true internal diameter (OR 0.75, 95% CI 0.66 to 0.85, p<0.001), younger age (OR 0.96, 95% CI 0.94 to 0.98; p<0.001) and larger body mass index (OR 1.05, 95% CI 1.01 to 1.09; p=0.02). The only corelate for significant MR was TMVIR (OR 7.90, 95% CI 4.01 to 15.56; p<0.001).

Significant residual MS (SHR 4.67; 95% CI 1.74 to 12.56; p=0.002) and significant residual MR (SHR 7.88; 95% CI 2.88 to 21.53; p<0.001) were both independently associated with repeat mitral valve replacement.

Study 4 Guerrero M (2020)

Study details

Study type	Retrospective registry analysis (NCT02245763-TVT registry)
Country	USA (at 172 hospitals)
Recruitment period	2013 to 2017
Study population and number	**N=903 high risk patients with (680 TMVIV versus 123 TMVIR versus TViMAC 100)** Median STS-PROM score, % overall 10 (6.6 to 16); TMVIV 10 (6.6 to 16.1); TMVIR 9.3 (6 to 14.4) TViMAC 10.3 (6.8 to 17.3); p= 0.290 NYHA class 3/4, %: overall 89.6 (n=801), TMVIV 90.5 (n=611), TMVIR 87.5 (n=105), TViMAC 85.9 (n=85) Mechanism of failure: mitral regurgitation [grade 3-4], %: overall 48.5 (n=433), TMVIV 45.6 (n=306), TMVIR 66.7 (n=82), TViMAC 45.5 (n=45) mitral stenosis, % overall 67.6 (n=598); TMVIV 69.2 (n=460); TMVIR 51.6 (n=63); TViMAC 76.5 (n=75); p<0.001
Age	Overall median age 75 years (range 67-82); 59.2% female
Patient selection criteria	High surgical risk patients who had clinically indicated TMVR with balloon-expandable aortic transcatheter heart valves were included. Patients who had the procedure under a research protocol were not included in this registry.
Technique	**Mean number of procedures per site** TMVIV- n=4.22; TMVIR-n=2.12; TViMAC- n=2.04 **Devices used:** overall Sapien (n=36), Sapien XT (n=364), Sapien 3 (n=468) and other (n=35) **Device size: (p=0.001)** Overall 23mm (n=90), 26mm (350), 29mm (439), missing (24) TMVIV 23mm (n=61), 26mm (249), 29mm (353), missing (17) TMVIR 23mm (n=16), 26mm (63), 29mm (39), missing (3) TViMAC 23mm (n=11), 26mm (38), 29mm (47), missing (4) **Access: (p=0.026)** Transapical-overall 44.8% (n=404); TMVIV 46.8% (n=318); TMVIR 35.8% (n=44); TViMAC 42% (42) Transseptal- overall 43.1% (n=389); TMVIV 41.8% (n=284); TMVIR 50.4% (n=62); TViMAC 43% (n=43) Other/unknown- overall 11.8% (n=107); TMVIV 11.3% (n=77); TMVIR 13.8% (n=17); TViMAC 13% (n=13)

	Procedure time (hours, median): overall 2.1; TMVIV 2.06; TMVIR 2.17; TVIMAC 2.42; p=0.0118 **Procedure status:** Overall: elective 76.2% (687); urgent 22.7% (205); emergency/salvage 1.1% (10) TMVIV: elective 74% (501), urgent 25% (170), emergency/salvage 1.7 (8) TMVIR: elective 84.6% (104), urgent 14.6 (18), emergency/salvage 0.8% (1) TViMAC: elective 82% (82), urgent 17% (17), emergency salvage 1% (1)
Follow-up	30 days
Conflict of interest/source of funding	This study was supported by the American College of Cardiology Foundation's National Cardiovascular Data Registry (NCDR) and the Society of Thoracic Surgeons National Database. Some authors have worked as consultants, proctors and received research grants from device companies.

Analysis

Follow-up issues: large number of missing follow-up data.

Study design issues: retrospective observational registry study, in-hospital and 30-day outcomes were evaluated. Study included real world data from large number of centres with a large sample size. Standardised definitions according to Valve Academic Research Consortium criteria were used to collect data. Primary outcomes were technical success, device success, procedural success at 30 days, in-hospital mortality and 30-day mortality. No standard definition of left ventricular outflow tract (LVOT) obstruction was used in this registry.

Study population issues: all patients had multiple comorbidities; TVIMAC patients were more likely to have had a prior aortic valve replacement (all=25%, TMVIV=22.1%, TMVIR=19.7%, and TVIMAC=50.2%; p<0.001). LVEF was lower in TMVIR patients. Trans-mitral gradients were higher in TMVIV or TVIMAC patients, and more mitral regurgitation was seen in TMVIR patients.

Other issues:

Key efficacy findings

- Number of patients analysed: 903 (680 TMVIV versus 123 TMVIR versus 100 TVIMAC)

Implantation and procedure outcomes

	Overall % (n=903)	TMVIV % (n=680)	TMVIR % (n=123)	TVIMAC % (n=100)	P value
Technical success^	87.9 (793/902)	90.9 (617/679)	82.9 (102/123)	74 (74/100)	<0.001
Device success*					
During procedure	94.1 (849/902)	95.1 (646/680)	93.5 (115/123)	88 (88/100)	<0.001

30 days	78.7 (n=485)	83.7 (n=386)	68.2 (n=58)	58.6 (n=41)	<0.001
Device technical failure	5.9 (53/902)	4.9 (33/680)	6.5 (8/123)	12 (12/100)	<0.001
Procedural success^^					
30 days	70.9 (n=445)	76.4 (n=359) ^^	59.5 (n=50)	48.6 (n=36)	<0.001

Denominator values were not available in the paper for 30-day outcomes.

^^technical success is exit from Cath lab by MVARC criteria (absence of procedural mortality; successful access, delivery, and retrieval of the device delivery system; successful deployment of the first intended device; and freedom from emergency surgery or re-intervention related to the device or access procedure).

*Device success at 30 days is defined as absence of procedural mortality or stroke; and freedom from unplanned surgical or interventional procedures related to the device or access procedure; and no residual mitral regurgitation greater than 1+.

^^Procedural success is measured at 30 days and is a composite of safety and efficacy end points defined as device success and absence of major clinical complications including: death, stroke, life-threatening bleed (by Valve Academic Research Consortium scale), major vascular complications, new stage 2 or 3 acute kidney injury including dialysis, myocardial infarction and absence of device-related dysfunction, migration, thrombosis, or other complications requiring surgery or repeat intervention.

Echocardiographic outcomes

	Overall	**TMVIV**	**TMVIR**	**TVMAC**	**P value**
Ejection fraction (%)					
Baseline	55 (47 to 62.5) (n=885)	55 (49 to 62) (n=665)	50 (35 to 58) (n=122)	60 (55 to 65) (n=98)	<0.001
30 days	55 (45 to 60) (n=460)	55 (45 to 60) (n=355)	45 (33 to 58) (n=54)	58 (53 to 67) (n=51)	<0.001
Mean mitral valve gradient, mmHg					
Baseline	11 (7 to 16) (n=885)	12 (8 to 17) (n=665)	7 (5 to 12) (n=122)	11 (7.5 to 13.5) (n=98)	<0.001
Post procedure	4 (2 to 5) (n=829)	4 (3 to 5) (n=632)	4 (2 to 5) (n=110)	4 (2 to 6) (n=87)	0.862
30 days	7 (5 to 9) (n=450)	7 (6 to 9) (n=348)	7 (6 to 9) (n=53)	6 (4 to 8) (n=49)	0.014
Mitral valve area, cm^2					

Baseline	1.3 (0.9 to 2.1) (n=885)	1.2 (0.8 to 1.9) (n=665)	1.8 (1.2 to 2.5) (n=122)	1.5 (1 to 2.5) (n=98)	<0.001
30 days	1.7 (1.4 to 2.3) (n=319)	1.7 (1.3 to 2.2) (n=249)	1.9 (1.5 to 2.4) (n=42)	1.9 (1.4 to 2.5) (n=28)	0.154

NYHA functional class

	Overall % (n=903)	**TMVIV % (n=680)**	**TMVIR % (n=123)**	**TVMAC % (n=100)**	**P value**
Baseline					**0.155**
1	1.6 (14)	1.3 (9)	0.8 (1)	4 (4)	
2	8.8 (79)	8.1 (55)	11.7 (14)	10.1 (10)	
3	55.1 (493)	54.4 (367)	55.8 (67)	59.6 (59)	
4	34.5 (308)	36.1 (244)	31.7 (38)	26.3 (26)	
30 days 0.007					
1	37.1 (176)	40.3 (146)	30.3 (20)	21.3 (10)	
2	44.8 (213)	43.9 (159)	51.5 (34)	42.6 (20)	
3	15.6 (74)	13.8 (50)	(16.7 (11)	27.7 (13)	
4	2.5 (12)	1.9 (7)	1.5 (1)	8.5 (4)	

Mitral regurgitation (MR)

	Overall % (n=903)	**TMVIV % (n=680)**	**TMVIR % (n=123)**	**TVMAC % (n=100)**	**P value**
Baseline					**<0.001**
None/trace	17.6 (93)	20.4 (137)	6.5 (8)	12.2 (12)	
Grade 1	19.5 (174)	20.1 (135)	11.4 (14)	25.3 (25)	
2	14.4 (129)	13.9 (93)	15.4 (19)	17.2 (17)	
3-4	48.5 (433)	45.6 (306)	66.7 (82)	45.5 (45)	
Residual MR post procedure					**<0.001**
None/trace	75.1 (675)	42.5 (557)	51.2 (63)	55 (55)	
Grade 1	19.3 (173)	13.8 (93)	35.8 (44)	36 (36)	
2	4.1 (37)	2.5 (17)	10.6 (13)	7 (7)	
3-4	1.4 (13)	1.1 (8)	2.4 (3)	0	
Residual MR at 30 days					**0.010**
None/trace	81.7 (374/458)	85.3 (300/352)	70.2 (38/54)	69.3 (36/52)	
Grade 1	15 (69/458)	12.8 (45/352)	20.4 (11/54)	25 (13/52)	

2-4	3.3 (15/458)	1.9 (7/352)	9.3 (5/54)	5.7 (3/352)	

No significant differences were seen between the MR and MS groups but MS patients in the TMVIR group had higher mean transmitral gradient (TMVIR MR 4.2 mmHg [n=21] versus mitral stenosis 6.7 mmHg [n=15], p=0.002).

Key safety findings

Complications and adverse events

	Overall % (n=903)	TMVIV % (n=680)	TMVIR % (n=123)	TVIMAC % (n=100)	P value
Procedural complications					
LVOT obstruction	2.3 (21/902)	0.7 (5/679)	4.9 (6/123)	10 (10/100)	<0.001
Conversion to surgery	1.6 (14/902)	1.3 (9/679)	2.4 (3/123)	2 (2/100)	0.579
Need for a second valve	3.7 (33/902)	1.5 (10/679)	7.3 (9/123)	14 (14/100)	<0.001
Cardiac perforation	2.1 (19/902)	1.9 (13/769)	2.4 (3/123)	3 (3/100)	0.798
New pacemaker need	1.2 (11/902)	1.2 (8/679)	0	3 (3/100)	0.106
Unplanned cardiac surgery/intervention	3 (27/902)	1.9 (13/679)	7.3 (9/123)	5 (5/100)	0.004
Unplanned vascular surgery/intervention	3 (27/902)	1.9 (13/679)	2.4 (3/123)	2 (2/100)	0.920
Vascular complications	3.3 (30/902)	2.9 (20/679)	4.9 (6/123)	4 (4/100)	0.518
Other in-hospital complications					
Major/life threatening bleeding	10 (89/902)	9.7 (65/679)	11.4 (14/123)	10.5 (10/100)	0.113
Cardiac arrest	4.7 (42/902)	3.8 (26/679)	4.9 (6/123)	10 (10/100)	0.022
Atrial fibrillation	2.5 (23/902)	2.2 (15/679)	2.4 (3/123)	5 (5/100)	0.279
Mortality: in-hospital					
All-cause related	8 (72/900)	6.3 (43/679)	9 (11/123)	18 (18/100)	0.004
Cardiovascular related	4.8 (43/900)	3.8 (26/677)	5.7 (7/123)	10 (10/100)	
Non-cardiovascular related	3.2 (29/900)	2.5 (17/677)	3.3 (4/123)	8 (8/100)	
Mortality -30 days					
All-cause related	10.1 (n=79)	8.1 (47/584)	8.1 (12/104)	21.8 (n=20)	0.003
Cardiovascular related	5.9 (n=46)	4.8 (28/584)	6.7 (7/104)	12 (n=11)	

IP overview: Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis

Non-cardiovascular related	4.2 (n=33)	3.3 (19/584)	4.8 (5/104)	9.8 (n=9)	
Stroke or TIA					
In-hospital	1.9 (17/902)	1.6 (11/679)	1.6 (2/123)	4 (4/100)	0.286
30 days	1.7 (n=11)	1.5 (n=7)	0	6.3 (n=4)	0.019
Myocardial infarction					
In-hospital	0.4 (4/902)	0.6 (4/679)	0	0	0.577
30 days	0.5 (n=3)	0.6 (n=3)	0	0	1.000
Valve embolisation					
During procedure	0.8 (7/902)	0.1 (1/679)	2.4 (3/123)	3 (3/100)	0.0805
30 days	0.8 (n=5)	0.2 (n=1)	3.6 (n=3)	1.6 (n=1)	0.014
Device migration					
During procedure	0.4 (4/902)	0.3 (2/697)	0	0.2 (2/100)	0.072
30 days	0.2 (n=1)	0.2 (n-1)	0	0	1
Mitral valve re-intervention					
During procedure	1.2 (11/902)	2.9 (20/679)	4.9 (6/123)	4 (4/100)	0.003
30 days	1.1 (n=7)	0.4 (n=2)	1.2 (n=1)	6.3 (n=4)	0.002
Septostomy closed					
During procedure	6.2 (56/902)	5.4 (37/679)	12.2 (15/123)	4 (4/100)	0.011
30 days	7.7 (n=49)	6.6 (n=32)	14.1 (n=12)	7.9 (n=5)	0.055
New requirement for dialysis					
In-hospital	3.9 (33/902)	3 (19/679)	6 (7/123)	8 (7/100)	0.034
30 days	1.9 (n=12)	1.7 (n=8)	2.4 (n=2)	3.1 (n=2)	0.767
Device thrombosis					
In-hospital	0	0	0	0	
30 days	0.2 (n=1)	0.2 (n=1)	0	0	1.0

Denominator values were not available in the paper for 30-day outcomes.

Study 5 Yoon SH (2019)

Study details

Study type	Retrospective registry analysis (TMVR international multicentre registry)
Country	USA (at 40 European and American centres)
Recruitment period	2009 to 2018
Study population and number	**N=521 patients at high risk for surgery had transcatheter mitral valve replacement (TMVR)** 1. **valve-in-valve (TMVIV, n=322)** for degenerated bioprostheses, 2. **valve-in-ring (TMVIR, n=141)** for failed annuloplasty rings, and 3. **valve-in-mitral annular calcification (TVIMAC, n=58)** for degenerated mitral valve with severe annular calcification Mean STS score, %: overall 9.0± 7.0% (TMVIV 9.2± 7.2% versus TMVIR 8.1± 6.4% versus TVIMAC 10.1± 6.9%; p=0.12) NYHA class 3/4, % (n): overall 88.5% (461), (TMVIV 87.6% (282), TMVIR 89.4% (126), TVIMAC 91.4 % (53); p=0.66) Mechanism of failure, % (n): mitral regurgitation: overall 45.7% (238) (TMVIV 36.6% (118), TMVIR 77.3% (109), TVIMAC 19% (11); p <0.001) mitral stenosis overall 33.2% (173) (TMVIV 40.7% (131); TMVIR 6.4% (9); TVIMAC 56.9% (33) combined: overall 21.1% (110) (TMVIV 22.7% (73), TMGVIR 16.3% (23), TVIMAC 24.1% (14)
Age and sex	Overall median age, (years) 72.6; (TMVIV 72.6, TMVIR 71.7, TVIMAC 74.7; p= 0.28) Female overall 54.1% (282) (TMVIV 58.7 (189), TMVIR 36.9 (52), TVIMAC 70.7 (41); p <0.001)
Patient selection criteria	Patients were considered for TMVR if they had significant dysfunction (either stenosis, regurgitation, or both) of a bioprosthetic mitral valve, annuloplasty ring, or a calcified mitral annulus, with comorbid conditions that would preclude a conventional mitral valve surgery.
Technique	All TMVR procedures were done using standard techniques. **Access route, % (n):** Transapical: overall 59.5% (310), TMVIV 59.9 (193), TMVIR 64.5 (91), TVIMAC 44.8 (26) Trans-septal: overall 39.5% (206), (TMVIV 38.8 (125), TMVIR 35.5 (50), TVIMAC 53.4 (31); p= 0.09) Transatrial: overall 1% (5), TMVIV 1.2 (4), TMVIR 0, TVIMAC 1.7 (1) **Devices used, % (n):** Sapien valves- (Sapien, Sapien XT, Sapien 3)

	Overall, 90% (469); (TMVIV 93.8% (302), TMVIR 85.1% (120), TVIMAC 81% (47), p <0.001) other -Melody, Lotus or Direct Flow **Device size, % (n):** Small overall 9.2% (48), TMVIV 8.7 (28), TMVIR 12.8 (18), TVIMAC 3.4 (2) Medium overall 37.6% (196), TMVIV 35.7 (115), TMVIR 44% (62), TVIMAC 32.8 (19) Large overall 53.2% (277), TMVIV 55.6 (179), TMVIR 43.3 (61), TVIMAC 63.8% (37)
Follow-up	30 days and 1 year
Conflict of interest/source of funding	Some authors have worked as consultants, proctors and received research grants or fees, honorarium, from device companies.

Analysis

Follow-up issues: follow up was done by clinical visits and telephone contacts.

Study design issues: large retrospective observational registry study, procedural and clinical outcomes of TMVIV, TMVIR, and TVIMAC were compared according to Mitral Valve Academic Research Consortium (MVARC) criteria. Data collected at prespecified time points was anonymised, centrally collected and any inconsistencies were resolved.

Study population issues: patients had multiple comorbidities. Baseline characteristics significantly differed across the 3 groups. The patients in TVIMAC group were more likely to be female and have NYHA functional Class 4 heart failure symptoms and chronic pulmonary disease, whereas patients in TMVIR group were more likely to have prior coronary artery bypass graft surgery (CABG) and myocardial infarction with lower left ventricular ejection fraction (LVEF). The predominant mechanism of failure was MR in the TMVIR group, but MS was the most frequent form of valve dysfunction in the TVIMAC group.

Other issues:

Key efficacy findings

- Number of patients analysed: 521 (322 TMVIV versus 141 TMVIR versus 58 TVIMAC)

Implantation and procedure outcomes

	Overall % (n=521)	**TMVIV % (n=322)**	**TMVIR % (n=141)**	**TVIMAC % (n=58)**	**P value**
Technical success^	87.1 (454)	94.4 (304)	80.9 (114)	62.1 (36)	<0.001
Device success*					
During procedure	77.2 (402)	84.8 (273)	69.5 (98)	53.4 (31)	<0.001
Procedural success^^					
30 days	65.8 (343)	73.6 (237)	57.4 (81)	41.4 (24)	<0.001

^^technical success is exit from Cath Lab by MVARC criteria (absence of procedural mortality; successful access, delivery, and retrieval of the device delivery system; successful deployment of the first intended device; and freedom from emergency surgery or re-intervention related to the device or access procedure).

*Device success at 30 days is defined as absence of procedural mortality or stroke; and freedom from unplanned surgical or interventional procedures related to the device or access procedure; and no residual mitral regurgitation greater than 1+.

^^Procedural success is measured at 30 days and is a composite of safety and efficacy end points defined as device success and absence of major clinical complications including: death, stroke, life-threatening bleed (by Valve Academic Research Consortium scale), major vascular complications, new stage 2 or 3 acute kidney injury including dialysis, myocardial infarction and absence of device-related dysfunction, migration, thrombosis, or other complications requiring surgery or repeat intervention.

Echocardiographic outcomes

	Overall (n=521)	**TMVIV (n=322)**	**TMVIR (n=141)**	**TVMAC (n=58)**	**P value**
Left ventricle ejection fraction (%)					
Baseline	52.6 ± 13.7	55.3 ± 11.5	44.3 ± 15.7	57.7 ± 10.7	<0.001
Post procedure	51.4 ± 13.7	53.3 ± 12.5	44.4 ± 14.7	58.0 ± 11.5	<0.001
Mitral valve gradient mm Hg (mean±SD)					
Baseline	10.9 ± 5.9	12.1 ± 5.9	7.1 ± 4.8	11.8 ± 4.8	<0.001
After procedure	6.1 ± 2.9	5.9 ± 2.8	6.7 ± 3.1	5.4 ± 3.1	0.019
Mean gradient >10 mm Hg	8.3 (n=43)	7.1 (n=23)	11.3 (n=16)	6.9 (n=4)	0.29
Mitral valve area, cm^2	2.2 ± 1.0	2.2 ± 1.2	2.0 ± 0.6	2.6 ± 1.1	0.10

Subgroup analysis-mode of failure

	Overall % (n=521)	**TMVIV % (n=322)**	**TMVIR % (n=141)**	**TVMAC % (n=58)**	**P value**
Mitral regurgitation (moderate or higher)					
Baseline	45.7 (238)	36.6 (118)	77.3 (109)	19 (11)	<0.001
After the procedure	10.0 (52)	5.6 (18)	18.4 (26)	13.8 (8)	<0.001
At 30 days	6.6 (31/467)	3.3 (10)	12.6 (16)	13.2 (5)	<0.001
Stenosis (mean transmitral gradient >10mmHg and/or an effective orifice area <1.0 cm^2).					
Baseline	33.2 (173)	40.7 (131)	6.4 (9)	56.9 (33)	
After the procedure	1.3 (7)	0.9 (3)	2.8 (4)	0	0.24

Key safety findings

Complications and adverse events

	Overall % (n=521)	TMVIV % (n=322)	TMVIR % (n=141)	TVMAC % (n=58)	P value
Procedural complications					
LVOT obstruction	7.1 (37)	2.2 (7)	5 (7)	39.7 (23)	<0.001
Conversion to surgery	2.3 (12)	0.9 (3)	2.8 (4)	8.6 (5)	0.004
Need for a second valve	5.4 (28)	2.5 (8)	12.1 (17)	5.2 (3)	<0.001
Valve embolisation	1.7 (9)	0.9 (3)	1.4 (2)	6.9 (4)	0.01
Left ventricular perforation	0.8 (4)	1.2 (4)	0	0	0.58
Reintervention	14.0 (73)	10.9 (35)	17.7 (25)	22.4 (13)	0.02
Paravalvular leak closure	3.5 (18)	2.2 (7)	7.8 (11)	0	0.006
Atrial septal defect closure	6.9 (36)	7.1 (23)	5 (7)	10.3 (6)	0.38
Alcohol septal ablation	1.9 (10)	0.6 (2)	0.7 (1)	12.1 (7)	<0.001
Mitral valve replacement	1.9 (10)	1.9 (6)	2.1 (3)	1.7 (1)	0.98
Surgery	1.5 (8)	1.2 (4)	2.1 (3)	1.7 (1)	0.77
Transcatheter MVR	0.4 (2)	0.6 (2)	0	0	>0.99
30-day outcomes					
All-cause mortality	10.4 (54)	6.2 (20)	9.9 (14)	34.5 (20)	<0.001
Stroke	1.9 (9)	2.3 (7)	0	3.9 (2)	0.10
Bleeding					
Major or extensive	4.2 (20)	4.6 (14)	3.9 (5)	1.8 (1)	0.81
Life threatening or fatal	3.7 (18)	2.3 (7)	6.7 (9)	4.5 (2)	0.07
Other					
Major vascular complication	2.8 (14)	1.6 (5)	3.8 (5)	8 (4)	0.019
Acute kidney injury (stage 2 or 3)	7.0 (34)	4.6 (14)	9.7 (13)	15.3 (7)	0.006
Mid-term all-cause mortality at 160 days (range 60-420 days)	22.8 (117/521)	16.4 (53/322)	24 (34/141)	51.7 (30/58)	
Late mortality at 1-year					
All-cause mortality	23.5%	30.6%	14%	62.8%	TMVIR versus TMVIV;

					adjusted HR 1.99, 95% CI 1.27–3.12; p= 0.003. TVIMAC versus TMVV; adjusted HR 5.29, 95% CI 3.29–8.51; p< 0.001.
Cardiovascular mortality	20.2	NR	NR	NR	
Clinical thrombosis at last follow-up*	n=11	n=10	n=1	0	
*The cumulative incidence of thrombosis was significantly higher in patients without anticoagulation compared with those with anticoagulation (6.6% vs. 1.6%; log-rank p=0.019). Patients with postprocedural MR moderate or above had significantly higher 1-year all-cause mortality compared with those with MR mild or less (41.5% vs. 21.4%; log rank p= 0.01).					

Study 6 Kamioka N (2018)

Study details

Study type	Retrospective comparative case series
Country	USA (at 3 centres)
Recruitment period	2007 to 2017 (VIV done from 2012)
Study population and number	**N=121** patients at high risk for surgery with severely degenerated bioprostheses **(62 transcatheter mitral valve-in-valve [TMVIV] implantation** versus **59 redo surgical mitral valve replacement [SMVR]).** Mean STS PROM score TMVIV 12.7 ± 8.0% versus SMVR 8.7±10.1%; p < 0.0001) Years after index surgery mean 10.3±8 years Mechanism of failure: mitral regurgitation: TMVIV 50%; mitral stenosis TMVIV 21%; combined: TMVIV 29%
Age and sex	Mean age TMVIV 74.9 years versus SMVR 63.7±14.9 years (p<0.001) 39% male in both groups (p=0.98).
Patient selection criteria	Included patients who had redo SMVR or TMVIV for previous mitral bioprosthetic valve failure. Excluded patents who had active endocarditis, required concomitant procedures for coronary artery disease or aortic disease, or underwent additional valve replacement.
Technique	All procedures and perioperative care were standard among operators and hospitals. All patients were prescribed anticoagulants or antiplatelets after the procedure. **TMVIV (n=62)** Approach: transapical (n=14) or transeptal (n=48) with apical rail in 5. Valve type: bioprosthesis (Sapien-7, Sapien XT 14, Sapien 3, 41) Concomitant percutaneous procedures: atrial septal defect closure (n=32), apical access percutaneous closure (n=3), percutaneous valvular leak closure (n=3), ablation for atrial fibrillation (n=1). **Redo SMVRs** (n=59) Approach: standard median sternotomy (n=40), thoracotomy/mini thoracotomy (n=19). One patient underwent robotic surgery through a mini thoracotomy. Valve type -47 bioprostheses (CEP Magna, Medtronic Mosaic/Hanock, St Jude Epic); 12 mechanical valves (St Jude, On-X). Concomitant surgical procedures: tricuspid valve repair (n=8), ablation for atrial fibrillation (n=6).
Follow-up	TMVIV group- median 285.5 days (range 112 to 494 days) SMVR group- median 930 days (range 152 to 1,596 days)

Conflict of interest/source of funding	Some authors received research grants, has been consultants/proctors for device companies.

Analysis

Follow-up issues: TMVIV follow-up data are limited; data from some patients was missing at discharge, 30-days and 1-year follow up.

Study design issues: retrospectively identified small number of patients; data were collected from medical records, local databases, or by phone contact. Baseline characteristics and outcomes were reported according to the Society of Thoracic Surgeons (STS) adult cardiac surgery data and Mitral Valve Academic Research Consortium (MVARC) criteria. Echocardiographic outcomes were reported according to the guidelines of the American Society of Echocardiography definition. 30 day and 1-year mortality was also assessed. Survival curves were analysed by the Kaplan–Meier method and compared with the log-rank test.

Study population issues: patients had multiple comorbidities and had some differences in baseline characteristics between the 2 groups. TMVIV patients were more likely to have lung disease (p=0.01), coronary artery disease (p=0.01), history of healed endocarditis (p=0.01), atrial fibrillation (p<0.001), and a history of a pacing device implantation (p=0.03), surgical procedure (CABG p=0.02; AVR p=0.01), than SMVR patients. There were no differences in baseline echocardiographic findings between the 2 groups.

Other issues: TMVIV technique evolved over study period.

Key efficacy findings

- Number of patients analysed: 521 (322 TMVIV versus 141 TMVIR versus 58 TVIMAC)

Implantation and procedure outcomes

	TMVIV % (n=62)	Redo SMVR % (n=59)	P value
Procedure time, mins	166.1± 66.2	427.7±102.7	<0.001
Intensive care unit stay, mins	39.9 ± 42.7	117.9±128.8	<0.001
Length of hospital stay, days	6.3 ±4.8	10.6±6.6	<0.001
Replacing valve inner diameter, mm	27.4 ± 1.7	26.1 ± 2.2	<0.001

Echocardiographic outcomes

	TMVIV % (n=62)	Redo SMVR % (n=59)	P value
Mean mitral valve gradient, mm Hg (mean ±SD)			
Baseline	12.1±5.2 (n=62)	13.9±6.7 (n=59)	0.35
Discharge	6.4 ± 2.4 (n=56)	6.9 ± 3.1 (n=21)	0.47

1 month	7.1 ± 2.5 (n=53)	6.5 ± 2.5 (n=18)	0.42
1 year	7.2 ± 2.7 (n=22)	5.5 ± 1.8 (n=24)	0.01
Mean aortic valve gradient, mm Hg (mean ±SD)			
Baseline	8.2 ±7.0 (n=62)	7.0 ± 5.4 (n=59)	0.96
Discharge	11.5±7.5 (n=56)	13.9±10.7 (n=21)	0.59
1 month	9.6±6.7 (n=53)	6.4±5.6 (n=18)	0.10
1 year	10.1±7.5 (n=22)	8.3±9.5 (n=24)	0.25
Mitral regurgitation (moderate or greater)			
Baseline	59.7 (37/62)	67.8 (40/59)	0.35
Discharge	7.1 (4/56)	0	0.21
1 month	3.8 (2/53)	5.6 (1/18)	1.00
1 year	4.5 (4/22)	4.1 (1/24)	1.00
Tricuspid regurgitation (moderate or greater)			
Baseline	62.9 (39/62)	54.2 (32/59)	0.33
Discharge	58.9 (33/56) 0	23.8 (5/21)	0.01
1 month	56.6 (30/53)	27.8 (5/18)	0.04
1 year	68.2 (15/22)	37.5 (9/24)	0.04
Aortic insufficiency (moderate or greater)			
Baseline	1.6 (1/62)	8.5 (5/59)	0.11
Discharge	1.8(1/21))	9.5 (2/56)	0.12
1 month	10.2 (5/53)	16.7 (2/18)	0.53
1 year	13.6 (3/22)	12.5 (3/24)	1.00
Left ventricular ejection fraction %			
Baseline	54.6±11.9 (n=62)	55.7±11.7 (n=59)	0.49
Discharge	52.4 ±13.3 (n=56)	50.4 ± 10.4 (n=21)	0.49
1 month	55.1±10.6 (n=53)	52.2 ± 12.8 (n=18)	0.32
1 year	52.8 ± 12.4 (n=22)	55.8±9.2 (n=24)	0.20

Key safety findings

Complications and adverse events

	TMVIV % (n=62)	Redo SMVR % (n=59)	P value
Mortality			
In-hospital death	3.2 (2/62)	3.4 (2/59)	1.00
30-day mortality	3.2 (2/62)	3.4 (2/59)	1.00
1-year mortality	11.3 (7/62)	11.9 (7/59)	0.92

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Vascular complications (in-hospital)			
Major vascular complication	1.6 (1/62)	5.1 (3/59)	0.36
Minor vascular complication	1.6 (1/62)	0	1.00
Bleeding (in-hospital)			
Life threatening bleeding	6.5 (4/62)	11.9 (7/59)	0.30
Major bleeding	8.1 (5/62)	33.9 (20/59)	<0.001
Minor bleeding	8.1 (5/62)	11.9 (7/59)	0.49
Stroke (in-hospital)			
Major stroke	0	3.4 (2/59)	0.24
Minor stroke	0	0	
LVOT obstruction*			
in-hospital	3.2 (2/62) *	0	0.16
Discharge	3.6 (2/56)	0	0.25
1 month	3.2 (2/53)	0	1.00
1 year	4.5 (/24)	0	1.00
Arrythmia (in-hospital)			
New complete heart block	0	5.1 (3/59)	0.07
New atrial fibrillation	1.6 (1/62)	30.5 (18/59)	<0.001
Prolonged ventilation >24 hours	4.8 (3/62)	33.9 (20/59)	<0.001
Valve thrombus			
1 month	1.9 (1/53)	0	1.00
1 year	0	0	

*defined as a case in which the gradient increased 10 mmHg from baseline according to the Mitral Valve Academic Research Consortium definition. Both patients were asymptomatic.

Study 7 Osman M (2020)

Study details

Study type	Retrospective comparative case series (propensity score matched)
Country	USA (data from national readmission database)
Recruitment period	2016 to 2017
Study population and number	**N=1,788** patients at high risk for surgery with severely degenerated bioprostheses **(384 transcatheter mitral valve-in-valve [TMVIV] implantation** versus **1,404 redo surgical mitral valve replacement [SMVR]).** Mean STS PROM score TMVIV 12.7 ± 8.0% versus SMVR 8.7±10.1%; p < 0.0001) Years after index surgery mean 10.3±8 years NYHA class 3/4: not reported Mechanism of failure: mitral regurgitation: TMVIV 50%; mitral stenosis TMVIV 21%; combined: TMVIV 29%
Age and sex	Mean age TMVIV 76 years versus SMVR 68 years (p<0.01) 56% female in both groups (p=0.76).
Patient selection criteria	Included patients aged ≥50 years with structural valve deterioration/degenerated mitral bioprosthesis, who had redo-MVR or TMVIV as per International Classification of Disease 10th-Clinical Modification codes. Excluded patients with infective endocarditis, patients with missing mortality data, and those who were transferred to another hospital to avoid duplication.
Technique	384 transcatheter mitral valve-in-valve [TMVIV] implantations 1,404 redo surgical mitral valve replacement [SMVR]. Access route: not reported (Further details were also not reported)
Follow-up	TMVIV group- 30 days SMVR group- 30 days
Conflict of interest/source of funding	Authors declare no known conflicts of interest.

Analysis

Follow-up issues: limited follow-up period.

Study design issues: retrospective study; data were collected from a national database. Lack of data on surgical techniques, valves used, echocardiography and haemodynamics/angiography. The primary end point was in-hospital mortality. Secondary end points were in-hospital major adverse events (MAEs); a composite of death, vascular complications, acute kidney injury, or stroke; length of stay, cost, and 30-day readmissions. To

account for differences in baseline characteristic, a parallel, balanced propensity-score matching was applied. A sensitivity analysis by excluding patients who underwent concomitant valve surgery was done.

Study population issues: patients had multiple comorbidities and those who underwent TMVIV were older (76 years versus 68 years, p<0.01) and had higher comorbidities.

Other issues: costs reported in the study were not extracted as its out of the remit of this overview.

Key efficacy and safety findings

- Number of patients analysed: 1,788 (384 TMVIV versus 1404 redo SMVR)

Clinical outcomes

	Unmatched cohort			Propensity score matched cohort		
	TMVIV	**Redo SMVR**	**P value**	**TMVIV**	**Redo SMVR**	**P value**
Major adverse events	25.8%	38.7%	<0.01	25.8%	44.1%	<0.01
Death	5.5%	9.5%	0.01	5.3%	11.9%	<0.01
Vascular complications	3.9%	5.9%	0.12	3.9%	6.4%	0.07
Acute kidney injury	21.1%	32.3%	<0.01	21.3%	35.6%	<0.01
Stroke	1%	1.1%	0.36	1.1%	1.4%	0.72
Blood transfusion	15.9%	34.8%	<0.01	15.2%	37.4%	<0.01
Length of hospitalisation, median, days	5 (2-11)	11 (7-18)	<0.01	5 (2-11)	11 (7-17)	<0.01
30-day readmission rate	14.7%	14.9%	0.95	14.7%	14.4%	0.92

In the sensitivity analysis, TMVIV remained associated with lower incidence of adjusted in-hospital mortality, but this did not achieve statistical significance (4.8% vs 8.0%, p = 0.06). However, adjusted MAEs continued to be significantly less with TMVIV (25.6% vs 40.0%, p <0.01).

Study 8 Murzi M (2017)

Study details

Study type	Retrospective comparative case series (propensity score matched)
Country	Italy (data from one centre)
Recruitment period	2005 to 2015
Study population and number	**N=61** patients at high risk for surgery with a failed mitral bioprosthesis **(40 right anterior minithoracotomy (MIMVR)** versus **21 transapical transcatheter mitral valve-in-valve (TMVIV) implantation)** EuroSCORE logistic TMVIV 39 ± 19 versus MIMVR 23±10; p < 0.005 LVEF %: TMVIV 50 ± 7 versus MIMVR 53±7; p < 0.225 NYHA class 3/4: TMVIV 85.7% (18/21) versus MIMVR 70.7% (29/40), p= 0.258 Mechanism of failure: not reported
Age and sex	Mean age TMVIV 77.9 years versus MIMVR 67 years (p=0.001) 61% (13/21) female in TMVIV group versus 56% (23/40) female in MIMVR group (p=0.51).
Patient selection criteria	Included patients who had reoperative mitral valve procedures for failed bioprostheses.
Technique	21 transapical transcatheter mitral valve-in-valve [TMVIV] implantations were done under general anaesthesia. 18 patients had a Sapien XT prosthesis (Edwards Lifesciences,). In 3 patients, Sapien 3 valve was used. 40 right thoracotomy mitral valve replacement- was performed with femoro-femoral bypass through a lateral right minithoracotomy. Aortic clamping and antegrade cardioplegia done in 36 patients. Conversion to sternotomy was necessary in 1 patient for bleeding. The mean diameter of the implanted valve was 26 ± 4mm in the MIMVR group and 26 ± 2mm in the M-VIV group (P = 0.8).
Follow-up	TMVIV group- median 15 ± 17 months MIMVR group- median 36 ± 29 months.
Conflict of interest/source of funding	None declared

Analysis

Follow-up issues: regular follow up at planned intervals and sometimes contacted by email or phone.

Study design issues: retrospective cohort study with small sample size; examined prospectively collected data from a database. Patients were assigned to best treatment options available by physicians. Treatment selection bias was adjusted by propensity score analysis and was included in the multivariate analysis.

Study population issues: patients who had TMVIV implantation were older (p = 0.03) and were more likely to have chronic kidney disease (p = 0.04), history of atrial fibrillation (p= 0.03) and pulmonary hypertension (p = 0.02) compared to MIMVR.

Other issues: costs reported in the study were not extracted as its out of the remit of this overview.

Key efficacy and safety findings

- Number of patients analysed: 61 (21 TMVIV versus 40 MIMVR)

Clinical outcomes

	TMVIV (n=21)	**MIMVR (n=40)**	**P value**
Technical success	(20/21)		
Mean trans-gradient post procedure, mm Hg	5.5 ± 2.1	5.8 ± 3.1	0.74
ICU stay, days	3±7	5±4	0.02
Hospital stay, days	9±7	14±7	0.03
Kaplan Meier event free survival at 2 years	86 ± 1%	87 ± 1%	0.148

Safety outcomes

	TMVIV (n=21)	**MIMVR (n=40)**	**Adjusted OR with 95% CI**	**P value**
In-hospital deaths	4.7 (1/21) *	7.5 (3/40) ^	2.46 (0.16–36.7)	0512
Late deaths	4/21|**	5/40^^		
Stroke	4.7 (1/21)	12.5 (5/40)	0.887 (0.48–16.2)	0.935
Low cardiac output syndrome	4.7 (1/21)	4.9 (2/40)	0.44 (0.23–8.77)	0.595
Renal dysfunction	4.7 (1/21)	10 (4/40)	0.511 (0.57–4.59)	0.549
Pulmonary complications	9.4 (2/21)	20 (8/40)	1.13 (0.16–7.81)	0.896
Reoperation for bleeding	4.7 (1/21)	14.6 (6/40)	0.427 (0.50–3.67)	0.438
Blood transfusion	23.5 (8/21)	35 (14/40)	0.934 (0.191–4.572)	0.933
Mild paravalvular leak	33 (7/21)	0		<0.001

*1 patient in the TMVIV group had intraoperative mitral valve migration resulting in acute severe subaortic

stenosis. The procedure was converted to open heart surgery for valve mispositioning, and the prosthesis was re-expanded, but the patient died of multiorgan failure.

** died of pneumonia, endocarditis, lung cancer and stroke at 1, 8, 18 and 46 months.

^Two patients in the MIMVR group died of postoperative multiorgan failure and 1 died of neurological complications.

^^ died of cardiac failure (3 patients), sudden cardiac death and stroke at 2, 6, 25, 43 and 57 months.

Study 9 da Costa LPN (2017)

Study details

Study type	Case series
Country	Brazil (data from one centre)
Recruitment period	2015 to 2018
Study population and number	**N=50** patients at high risk for surgery had **transapical transcatheter mitral valve-in-valve (TMVIV) implantation)** mean STS scores and EuroSCORE II were 8.3% and 12.4%, Time since previous surgery, years: 12.1±5.4 NYHA class 3/4: 80% (40/50) Aetiology of mitral valve disease: 64% had rheumatic disease; 6% had mitral regurgitation because of valve prolapse; and 30% had conditions from other causes (i.e. endocarditis, ischaemia). Mechanism of failure: mixed 11 (n=22), regurgitation 15 (n=30), stenosis 24 (n=48) Urgent procedures in those with severe heart failure 36% (18/50)
Age and sex	Mean age 64.8 years; 72% female
Patient selection criteria	Included patients who had reoperative mitral valve procedures for failed bioprostheses.
Technique	TMVIV -all patients were operated on and received a balloon-expandable valve via the transapical approach. A 6-Fr temporary pacing catheter was placed in the right ventricle via the right femoral vein for rapid pacing during THV deployment. A THV Braile Inovare size 30 was used in 34% of cases, size 28 in 40%, size 26 in 24%; only 1 valve size 24 was used.
Follow-up	median follow-up period was 7 (3 to 13) months, with the longest follow up 854 days. 1-year follow up in 25 patients
Conflict of interest/source of funding	Half of the THVs used in this study were donated by Braile Biomedica. Primary author received financial support from the company to present the findings at a conference.

Analysis

Follow-up issues: regular follow up at planned intervals; one patient was lost to follow up and 1 patient who moved to a distant city was discharged from follow up.

Study design issues: prospective database analysis; outcomes were analysed and compared between first and second 25 patients to assess the impact of learning curve. Outcomes and follow-up data were analysed retrospectively according to the Mitral Valve Academic Research Consortium Part 2 standardized end point definitions

Study population issues: Patients were younger, had multiple previous open heart operations and rheumatic disease. Atrial fibrillation was very common, severe pulmonary hypertension was seen in 40%, associated coronary artery disease (CAD) was coronary artery bypass graft (CABG) were uncommon, 18% and 10%. 42% had just 1 previous MVR; 36% had 2 previous operations; and 22% had >3 previous operations (with as many as 5 previous surgical interventions).

Other issues:

Key efficacy and safety findings

- Number of patients analysed: 50 TMVIV

Echocardiographic data

	Baseline (n=50)	**Post-operative (n=44)**	**P value**
Mean LVEF (%),	59.2±10.2	56.1±12.7	0.036
Mean mitral valve area (cm2)	1.2±0.5	1.8±0.6	0.022
Mean gradient (mmHg)	11.5±5.5	6.4±2.6	<0.001
Maximum gradient (mmHg)	23.5 ±7.1	14.6 ±4.6	<0.001
Pulmonary artery systolic pressure, (mmHg)	58.6 ±17.5	49.8 ±12.8	0.011
Mitral regurgitation			0.001
0	6% (3)	18.2 (8)	
1	18 (9)	63.6 (28)	
2	6 (3)	18.2 (8)	
3	12 (6)	0	
4	58 (29)	0	

Clinical outcomes at 30 days follow-up

	% (n=50)
Successful implantation	98%
ICU length of stay (days), medians (IQR)	5 (3 to 11)
Postoperative length of stay (days), medians (IQR)	9 (6 to 17.25)
Total length of stay (days), medians (IQR)	15 (9 to 28.9)
NYHA functional class at 30 days, n (%)	
Class 1	67.4% (29/50)
Class 2	28 (12/50)
Class 3	2.3 (1/50)

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Class 4	2.3 (1/50)
Myocardial infarction	4 (2/50)
Major vascular complication	6 (3/50)
Major bleeding	4 (2/50)
Stroke	2 (1/50)
Acute renal failure	30 (15/50)
Sepsis	28 (14/50)
Death	14 (7/50)
Intraoperative deaths*	2 (1/50)
Death at 30-days^	12 (6/50)
Late deaths (3 to 13 months)	0
Leaflet thrombosis (managed with anticoagulation)	n=1
Infective endocarditis (at 6.5 months, managed with antibiotics)	N=1
Mitral regurgitation %	
Absent or minimal	81.8%
Mild	18.2%
Moderate or severe	0

* valve embolisation into the left ventricle in a patient was noted, an emergency open surgery was done, but patient died at the end of the procedure.

^One patient had major bleeding with cardiac tamponade and multiple organ dysfunction, leading to death on 8th postoperative day; 5 patients developed septic shock, with prolonged intubation and ICU stays, and died on postoperative days 11, 15, 26, 26 and 28.

Study 10 & 11 Cheung A (2013), Cheung A (2011)

Study details

Study type	**Prospective case series**
Country	Canada (single centre)
Recruitment period	2007 to 2012
Study population and number	n=**23** patients with severe mitral prosthetic valve dysfunction **Mean STS score:** 12.1%±6.9%. **NHYA class:** 96% (22/23) 3/4; 4% (1/23) class 2. **Type of failed devices:** Carpentier–Edwards Perimount (n=6), St Jude (n=1); Medtronic Mosaic (n=8), Edwards Porcine (n=8). **Failed valve size:** 23 mm (n=2), 25 mm (n=6); 27 mm (n=8); 29 mm (n=5); 31 mm (n=1); 33 mm (n=1). **Failure mode:** Stenosis 30% (7/23); regurgitation 39% (9/23); both stenosis and regurgitation 30% (7/23). **Time to failure:** median 10 years (range 8--0) after bioprosthesis implantation.
Age and sex	Mean 81±6 years; 61% (14/23) female.
Patient selection criteria	Symptomatic patients with severe heart failure and structural mitral prosthetic valve dysfunctions deemed unsuitable for reoperative mitral valve surgery because of high risk (according to American College of Cardiology/American Heart Association).
Technique	**Transapical transcatheter mitral valve-in-valve implantation** done as described above (in procedure description). Device: balloon expandable Edwards SAPIEN (n=12); SAPIEN XT (n=10); Cribier-Edwards equine valve (n=1). Size: 23 mm (n=5); 26 mm (n=13); 29 mm (n=5) in diameter Approach: Transapical 100% General anaesthesia used, guided by fluoroscopy and TEE; TEE analysis was performed preoperatively, before discharge, at 6 and 12 months and then annually. Clinical follow-up was done by the implantation team or local physician. Balloon valvuloplasty used in only first patient; Cardiopulmonary support was not used. 65% had anticoagulation and single antiplatelet therapy; 30% were given dual antiplatelet therapy and one was given only warfarin.
Follow-up	**mean 753 days (range 376-1119 days)**
Conflict of interest/source of funding	Five authors are consultants to Edwards. One author is part of the Speaker's Bureau; one author received grant and one received consultant fees.

Analysis

Follow-up issues: complete follow up.

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Study design issues: procedures were done on compassionate basis to patients not suitable for surgery; procedural success and complications were reported according to Valve Academic Research Consortium-2.

Study population issues: 2 patients had native aortic stenosis and mitral valve regurgitation had concomitant aortic and mitral valve implantations.

Other issues: patients from study 11 are included in study 10. But some of the safety data are reported from study 11.

Key efficacy and safety findings

- Number of patients analysed: 23 TMVIV

Procedure success: 100% (according to VARC-2 definition- without access site complications, or procedural mortality)

(In 1 procedure, implantation initially through the left atrium through a right thoracotomy was unsuccessful [the delivery system failed to align properly] and was converted to a left thoracotomy and transapical approach).

Survival: All patients were alive at 30-day follow up. At a median follow up of 753 days (range 376 to 1119 days), Kaplan–Meier survival rate was 90.4% with the longest follow up of 1,448 days.

NYHA class: 95.6% (22/23) of the patients clinically improved to NYHA class 1/2 at last follow up. One patient with hypertrophic obstructive cardiomyopathy had septal ablation after the procedure with only minimal improvement and continued to be in NYHA class 3 despite satisfactory valve function.

Valvular performance: The median postprocedural transvalvular gradient was 7 mmHg (range 5 to 8 mmHg) and minimal transvalvular (1+) or paravalvular regurgitation was seen. All patients had satisfactory hemodynamic and valvular function.

	Baseline (n = 23)	At discharge (n = 23)	p value
Transvalvular mean gradient (mmHg)*	11.1±4.6	6.9±2.2	0.014
Valvular regurgitation^ (Grade) (n)	Grade 4 (n=14) Grade 3 (n=4) Grade 2 (n=3) Grade 1 (n=1)	Grade 3,4 (0) Grade 2 (52.2% n=12) Grade I (47.8% n=10)	

^Valvular regurgitation graded as grade 4 (severe), grade 3 (moderate), grade 2 (mild), grade 1 (trivial) and grade 0 (none).

At last follow-up, no patient had moderate or severe mitral regurgitation.

Safety events

Complication	% (n = 23)
Intraprocedural mortality	0
Mortality at 30 days	0
Mortality at last follow-up (median 753 days) (1 death on day 45 with respiratory failure and 1 on day 135 unknown cause; defined as cardiovascular according VARC-2*)	9.6 (2/23)
Intraprocedural valve embolization or malpositioning	0
Structural valve failure or embolisation	0
Reoperation for bleeding or tamponade	0
Major periprocedural stroke (complicated by nosocomial pneumonia and renal failure needing temporary haemodialysis; prolonged intensive care stay and died on day 45 with respiratory failure, despite renal and neurological recovery)	4.4 (1/23)
Major bleeding	26 (6/23)
Myocardial Infarction	0
Acute kidney injury (stage 3 by VARC-2; 1 needed temporary renal replacement therapy)	8.7 (2/23)
Permanent pacemaker implantation (on day 3 for pre-existing atrioventricular conduction disturbance)	4.4 (1/23)
Reintervention (at 2 months, because of acute heart failure 4 to5 mm atrial migration of the valve was noted on echocardiogram and a second transapical transcatheter mitral valve-in-valve implantation was done with no complications or valvular regurgitation).	4.4 (1/23)
Paravalvular regurgitation	0
Apical haemorrhage	0
Haemothorax (drained with a thoracostomy tube)	4 (1/23)
Incisional haematoma	4 (1/23)
Atrial clot (detected at 6-month follow up echocardiogram; patient was asymptomatic with no embolic events but treated with systemic anticoagulation)	4 (1/23)

*with pleural effusions and poor mobility.

Validity and generalisability of the studies

- There are no randomised controlled studies comparing transapical TMVIV with current standard (surgical mitral valve replacement). Only 2 small retrospective studies comparing transapical TMVIV for deteriorated bioprosthetic valves with redo mitral valve surgery were included (Kamioka 2018, Murzi 2017). Another included study compared TMVIV implantation with redo mitral valve surgery but did not specify the access route (Osman 2020).
- Evidence on transapical TMVIV implantation is mainly from published observational studies and retrospective registry analyses.
- 60% of patients included in registry analyses and systematic reviews had TMVIV implantations via transapical access and 40% via transseptal access (Hu 2018, Takagi 2018, Simonato 2020, Guerrero 2020, Yoon 2019).
- Evidence has been stratified and presented according to access routes in 1 systematic review (Hu 2018). Meta-analysis of risk ratios for 30-day mortality in transapical TMVIV implantations has been presented in another systematic review (Takagi 2018). One registry analysis presented sub-group analysis for survival according to access route (Simonato 2020).
- There is no long-term evidence on the efficacy and safety of this procedure.
- There may be some overlap of patients in the TMR, TVT, and VIVID registry data and with those in studies added to systematic reviews. In total, 302 centres in Europe and North America contributed their valve-in-valve experience to the registries (Simonato 2020, Guerrero 2020, Yoon 2019).
- Grading systems for assessment of mitral regurgitation were not clearly described in the primary papers added to the systematic reviews.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Percutaneous mitral valve leaflet repair for mitral regurgitation NICE interventional procedure guidance 649 (2019). Available from http://www.nice.org.uk/guidance/IPG649
- Transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction. NICE interventional procedure guidance 504 (2014). Available from http://www.nice.org.uk/guidance/IPG504
- Transcatheter aortic valve implantation for aortic stenosis. NICE interventional procedure guidance 421 (2012). Available from http://www.nice.org.uk/guidance/IPG421
- Percutaneous mitral valve annuloplasty. NICE interventional procedure guidance 352 (2010). Available from http://www.nice.org.uk/guidance/IPG352
- Percutaneous mitral valve leaflet repair for mitral regurgitation. NICE interventional procedure guidance 309 (2009). Available from http://www.nice.org.uk/guidance/IPG309
- Thoracoscopically assisted mitral valve surgery. NICE interventional procedure guidance 245 (2007). Available from http://www.nice.org.uk/guidance/IPG245
- Balloon valvuloplasty for aortic valve stenosis in adults and children. NICE interventional procedure guidance 78 (2004). Available from http://www.nice.org.uk/guidance/IPG78
- Non-surgical reduction of the myocardial septum. NICE interventional procedure guidance 40 (2004). Available from http://www.nice.org.uk/guidance/IPG40

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. No Professional expert questionnaires for transapical transcatheter mitral valve-in-valve implantation for a failed surgically-implanted mitral valve bioprosthesis were submitted.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received no completed submissions.

Issues for consideration by IPAC

Ongoing studies

- NCT03193801 PARTNER 3 Trial - mitral valve in valve is a prospective, single-arm, multi-center study to investigate the safety and effectiveness of SAPIEN 3 transcatheter heart valve implantation in patients with a failing mitral bioprosthetic valve (Device: Edwards SAPIEN 3 transcatheter valve), n=50 patients, single group assignment; location: USA; primary completion date August 2020, study completion date August 2024.

- NCT 02370511 Mitral Implantation of Transcatheter Valves (MITRAL) The Safety and Feasibility of the SAPIEN XTTM Transcatheter Heart Valve With NovaFlex and Ascendra Delivery Systems and SAPIEN 3 with commander delivery system in patients with symptomatic severe calcific mitral valve disease with severe mitral annular calcification and patients with failing mitral surgical rings or bioprostheses who are not candidates for mitral valve surgery. TMVIV, TMVIR, and TVIMAC is being evaluated in this prospective early feasibility clinical trial. N=91; The primary safety endpoint is technical success at exit from the Cath lab; primary performance endpoint: absence of MR grade 2 (+) or greater or mean MVG ≥10 mmHg at 30 days and 1 year. study completion date 2022; location USA.

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2. Takagi H, Hari Y, Kawai N et al (2018) meta-analysis of valve-in-valve and valve-in-ring transcatheter mitral valve implantation. J Interv Cardiol; 31:899–906.
3. Simonato M, Whisenant B, Ribeiro HB et al. (2020) Transcatheter mitral valve replacement after surgical repair or replacement: comprehensive mid-term evaluation of valve-in-valve and valve-in-ring implantation from the VIVID registry. 10.1161/CIRCULATIONAHA.120.049088
4. Guerrero M, Vemulapalli S, Xiang Q et al. (2020) 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. Circ Cardiovasc Interv. 13: e008425.
5. Yoon SH, Whisenant BK, Bleiziffer S et al. (2019) Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. European Heart Journal, 40, 441–451.
6. Kamioka N, Babaliaros V, Morse MA et al. (2018) Comparison of clinical and echocardiographic outcomes after surgical redo mitral valve replacement and transcatheter mitral valve-in-valve therapy. JACC Cardiovascular Interventions 11,12: 1131-8
7. Osman M and Al-Hijji MA (2020) Comparative outcomes of mitral valve in valve implantation versus redo mitral valve replacement for degenerated bioprotheses. The American journal of cardiology. 132:175-176
8. Da Costa LPN, Palma JH, Barbosa Ribeiro H et al (2020) Transcatheter mitral valve-in-valve implantation: reports of the first 50 cases from a Latin American Centre. Interactive CardioVascular and Thoracic Surgery 30, 229–235.
9. Murzi M, Berti S, Gasbarri T et al. (2017) Transapical transcatheter mitral valve-in-valve implantation versus minimally invasive surgery for failed mitral bioprostheses. Interact CardioVasc Thorac Surg; 25:57–61.
10. Cheung A, Webb JG et al (2013). 5-year experience with transcatheter transapical mitral valve-in-valve implantation for bioprosthetic valve dysfunction. Journal of the American College of Cardiology 61: 1759-66.

11. Cheung AW, Gurvitch R, Ye, J et al (2011). Transcatheter transapical mitral valve-in-valve implantations for a failed bioprosthesis: a case series. Journal of Thoracic & Cardiovascular Surgery 141: 711-715.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	03/08/2020	Issue 8 of 12, August 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	03/08/2020	Issue 8 of 12, August 2020
MEDLINE (Ovid)	03/08/2020	1946 to July 31, 2020
MEDLINE In-Process (Ovid)	03/08/2020	1946 to July 31, 2020
MEDLINE Epubs ahead of print (Ovid)	03/08/2020	July 31, 2020
EMBASE (Ovid)	03/08/2020	1974 to 2020 Week 31

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 Mitral Valve Stenosis/
2 Mitral Valve Insufficiency/
3 (mitral* adj4 (stenos* or insufficien* or incompeten* or regurgitat* or disease* or dysfunct* or malfunct* or degenerat* or position*)).tw.
4 or/1-3
5 Mitral Valve/
6 (mitral adj2 valve*).tw.
7 MVR.tw.
8 heart valve prosthesis implantation/ or Heart Valve Prosthesis/
9 ((Artificial* or prosthe* or tissue* or bicuspid* or left atrioventricular*) adj4 valve*).tw.
10 bioprosthesis/
11 bioprosthe*.tw.
12 or/5-11
13 prosthesis failure/
14 (fail* or dysfunct* or replace* or malfunct* or degenerat* or insufficien* or incompeten* or regurgitat*).tw.
15 Reoperation/
16 (Reoperat* or Re-operat*).tw.
17 or/13-16

18 "valve in valve".tw.
19 (balloon adj4 expandable*).tw.
20 ((Cribier* or Carpentier*) adj2 Edwards).tw.
21 (corevalve or medtronic).tw.
22 (edwards adj4 (sapien or mitral)).tw.
23 fortis.tw.
24 ((transcatheter or transapic*) adj4 (valve* or replace* or implant*)).tw.
25 (TVIV or TVR or THV).tw.
26 or/18-25
27 4 and 12 and 17 and 26
28 animals/ not humans/
29 27 not 28
30 limit 29 to ed=20200318-20200831

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Baldizon I, Spinoza A, Kuntze T et al. (2016) Early transcatheter valve dysfunction after transapical mitral valve-in-valve implantation. Interactive Cardiovascular and Thoracic Surgery 22, 501–503	Case report N=1 Transapical mitral valve-in-valve procedure.	Early thrombotic transcatheter mitral valve dysfunction occurred on oral anticoagulation with Coumadin in combination with antiplatelet therapy. This associated with an extensive left atrial thrombus formation. The bioprostheses were removed and a new valve implanted.	Safety event already reported in studies added to table 2.
Cerillo Ag, Chiaramonti F et al (2011). Transcatheter valve	Case series n=4 failure of bioprosthesis (3	The first mitral procedure was complicated by the splaying of the	Larger and longer follow-up studies included in table 2.

in valve implantation for failed mitral and tricuspid bioprosthesis. Catheter Cardiovasc Interv. 78: 987-995	mitral and 1 tricuspid) Transapical transcatheter valve in valve implantation for mitral valves. 26mm Sapien valve used.	xenograft stents and embolization of the valve. The procedure was converted to conventional surgery, and the patient died on postoperative day 1. In the subsequent procedures, the valve was positioned more atrially, and was fixed to the malfunctioning xenograft sewing ring. Three procedures were successful, all patients were discharged home and were alive and well at follow-up.	
Cerillo AG, Gasbarri T, Celi S, et al. (2016) Transapical transcatheter valve in- valve implantation for failed mitral bioprostheses: gradient, symptoms, and functional status in 18 high-risk patients up to 5 years. Ann Thorac Surg. 102:1289–1295.	Case series N=18 patients at high risk had mitral valve-in valve implantation for failed mitral bioprostheses. Follow-up up to 5 years.	In 1 patient, the transcatheter valve embolized in the ventricle. The patient died 2 days later of multiorgan failure. There were no other hospital deaths. 4 patients died of pneumonia, endocarditis, lung cancer, and stroke at 1, 8, 18, and 46 months. The mean gradient at discharge was 5.1 ± 2.3 mm Hg. At median 27 months, all patients were in NYHA functional class II or I. The mean transprosthetic	Study included in systematic review added to table 2.

		gradient was 7 mm Hg.	
Codner P, Assali A, Vaknin-Assa H et al (2015). Treatment of aortic, mitral, and tricuspid structural bioprosthetic valve deterioration using the valve in valve technique. The Journal of Heart Valve Disease. 24 (3), 345-352.	Case series N=33 (of which 10 mitral VIV implantations) Edwards Sapien valve via transapical access. Follow-up 2 years.	100% valve implantation success. One patient died 40 days later due to pneumonia and sepsis. All patients were in NYHA class I and II. Absence of grade I mitral regurgitation in 100% cases. Survival rates were 75% at one and years follow-up.	Larger and longer follow-up studies included in table 2. Also included implantations in aortic, pulmonary and tricuspid positions.
Condado JF, Kaebnick B, Babaliaros V. (2016) Transcatheter Mitral Valve-in-Valve Therapy. 5 (1), 117-123.	Review	VIV-TMVR and VIR-TMVR have reported success rates of 70% to 100%. This article discusses the unique technical challenges of VIV-TMVR emerging from the complex mitral valve anatomy and limitations of existing technology.	Review
Conradi L, Silaschi M, Seiffert M, et al. (2015) Transcatheter valve-in-valve therapy using 6 different devices in 4 anatomic positions: clinical outcomes and technical considerations. J Thorac Cardiovasc	Retrospective case series N=75 patients had ViV procedures for failure of surgical bioprostheses. ViV was performed in aortic (72.0%, 54/75), mitral (22.7%, 17/75), tricuspid (2.7%, 2/75), and	ViV can be performed in all anatomic positions with acceptable hemodynamic and clinical outcome in high-risk patients. Increasing importance of ViV can be anticipated considering growing use of surgical bioprostheses.	Study included in systematic review added to table 2. Study also included data on VIV implantations in other positions (aortic, pulmonary, tricuspid).

Surg.150:1557–1567	pulmonary (2.7%, 2/75) positions.		
Dahle G, Rein K-A, Fiane AE. (2017) Single centre experience with transapical transcatheter mitral valve implantation. Interact Cardiovascular Thorac Surg; 25:177–84.	Case series N=11 patients -with 2 failed bioprostheses, 6 failed repair annuloplasty rings, 3 in the native valve all at high risk for open mitral valve surgery. Follow-up 30- days	Implantation success was 100%. Good haemodynamics and improved NYHA class seen in all patients. One patient died before 30 days due to sepsis. One patient had a valve thrombosis and had a second valve implanted into the first one as a 'valve-in-valve' procedure.	Larger and longer follow-up studies included in table 2. Study also included implantations in annuloplasty ring and native valves. Outcomes were not reported separately.
D'Onofrio A, Tarja E, Besola L, et al. (2016) Early and midterm clinical and hemodynamic outcomes of transcatheter valve-in-Valve implantation: results from a multicenter experience. Ann Thorac Surg. 102:1966–1973	Case series N=65 VIV procedures (in aortic position =44 and **mitral position=22-transapical**) Mean follow-up 12 months (in mitral group)	2 deaths (9%) were reported in mitral group at follow-up. Causes of death were rupture of the left ventricular apex with massive bleeding in 1 patient and intraprocedural ventricular embolization during VIV-M that required immediate conversion to conventional surgery and death for multiorgan failure 4 days after the operation. Survival at 3 years of VIV-M patients was 90.9%. Peak and mean gradients16 mm Hg and 7 mm Hg.	Study included in systematic review added to table 2. Study also reported data on 44 VIV procedures in aortic position (which is out of the scope of this report).
D'Onofrio A, Gallo M, Tarantini G, et al. An unexpected finding: stuck	Case series N=1 TMVIV 1-year follow-up	At the 6-month follow-up, one of the three pericardial leaflets were stuck in the	Safety event already reported in systematic reviews added to table 2.

leaflet after transapical mitral valve-in-valve implantation. JACC Cardiovasc Interv. 2014;7: e187–e189.		closed position; however, the patient was in excellent clinical condition. Fluoroscopy showed an “hour-glass” shape of the SAPIEN XT valve due to a final positioning that favoured the atrial side (30% to 35% on the atrial side.	
Elmously A, Worku B, Gray KD, et al. (2018) Mitral valve-in-valve implantation as an elective or rescue procedure in high risk patients. Ann Thorac Surg. 105:1778–1783	Case series (retrospective) N=19 patients (including 12 with cardiogenic shock) with bioprosthetic mitral valve failure had TA-MVIVI with an Edwards Sapien prosthesis Mean follow-up 339 days (range, 30 to 1291).	TA-MVIV implantation was successful in all with no deaths, strokes, or myocardial infarctions at 30 days. 2 had brief cardiac arrest but recovered. Mean transmitral gradient decreased from 12 ± 5 mm Hg to 5 ± 3 mm Hg (p= 0.0005). death from unknown cause reported within first year (5.2%). Trace transvalvular regurgitation developed in 15.8% (3/19) patients. 89.5% of patients were NYHA class I or II.	Study included in systematic review added to table 2
Gaia DF, Braz AM, Simonato M, et al. (2017) Mitral implant of the Inovare transcatheter heart valve in failed surgical bioprostheses: a	Case series N=11 transapical mitral ViV approach using the Braile Inovare prosthesis for a failed mitral bioprosthesis.	Successful valve implantation was done in all. In one case, a right lateral thoracotomy was performed for the removal of an embolized prosthesis. There	Study included in systematic review added to table 2.

novel alternative for valve-in-valve procedures. Interact Cardiovasc Thorac Surg; 24:514–520.	Follow=up 1-30 months.	was no operative mortality. 30-day mortality was 8.3%. Ejection fraction was preserved after the implant p = 0.3. The mitral gradient showed a significant reduction p < 0.001. Residual mitral regurgitation was not present. There was no left ventricular outflow tract obstruction.	
Gallo M, Dvir D, Demertzis S et al. (2016) Transcatheter valve-in-valve implantation for degenerated bioprosthetic aortic and mitral valves. Expert Review of Medical Devices, Vol 13, 8, 749–758.	Review of transcatheter VIV implantation for degenerated bioprosthetic aortic and mitral valves.	reviewed the clinical outcomes and the procedural details of published transcatheter aortic and mitral valve-in-valve series focusing on data from the Valve-in-Valve International Data registry (VIVID), and we provide a practical guide for valve sizing and stent-valve positioning	Review
Flynn CD, Wilson-Smith AR, Yan TD. (2018) Novel mitral valve technologies - transcatheter mitral valve implantation: a systematic review. Ann Cardiothorac Surg; 7(6):716-723	Systematic review of 25 studies (112 patients) assessing the outcomes of patients undergoing transcatheter mitral valve implantation (using 6 valves) for native mitral regurgitation or failed prior surgical repair or bioprosthetic replacement.	The mean postoperative gradient was 5.4±3.0 mmHg. There were 3 early deaths (7%) and total mortality of 10 patients (23%) at a mean of 163 days post-operatively. The average hospital length of stay was 15.4±15.1 days. One patient required emergency cardiac surgery to	Native valve and bioprosthetic failures were treated with VIV and VIR implantations. More comprehensive and updated systematic reviews were included in table 2.

	VIV (N=44 in 8 studies) transapical in 90% VIR (n=20) Follow-up =197 days.	salvage an embolized prosthesis, who later died.	
Joseph TA, Eleid MF, Cabalka AK et al. (2019) Long term outcomes of melody valve in valve implantation for bioprosthetic mitral valve dysfunction. Catheterization and cardiovascular interventions. 93 (6), 1087-1094.	Case series N=13 patients who underwent Melody valve-in-valve for bioprosthetic dysfunction. Median follow-up was 4.5 years with longest follow-up of 5.5 years.	30-day mortality was 15.4% with 1-year mortality of 25% and no other reported deaths until 4.5 years. 76.9% of patients had mitral gradient of 5 mmHg or less post procedure. One patient required repeat valve procedure for structural deterioration at 4.4 years. At 1, 3, and 5-year follow-ups 75% of patients were NYHA class 1 or 2, mean gradients were 4.5, 6.8, and 7.5, respectively. Mitral regurgitation post procedure was 0.8. At 1, 3, and 5 years this increased to 1.0, 1.3, and 2.5, respectively.	Larger studies added to table 2.
Leone A, Alfonsi J, Pilato E et al. (2018) Transcatheter mitral valve-in-valve dislocation: A rescue strategy. Ann Thorac Surg; 106: e137–9.	Case report N=1 Transapical valve-in-valve mitral valve implantation with degenerated mitral bioprosthesis.	Fatal complication of the mitral prosthesis migration into the aortic arch was reported. The dislocated prosthesis was successfully stabilized in	Safety event already reported in systematic reviews added to table 2.

		the aortic arch with a bare aortic stent, ensuring adequate perfusion of aortic vessels.	
Mankad SV, Aldea GS, Ho N. (2018) Transcatheter Mitral Valve Implantation in Degenerated Bioprosthetic Valves. J Am Soc Echocardiogr; 31:845-59.	Review	Review is focused on the echocardiographic evaluation required pre, intra, and post-procedurally during transcatheter mitral valve insertion.	Review
Medranda GA, Bramhbhatt K, Marzo K et al. (2020) Outcome of Patients Having Transcatheter Mitral Valve Implantation for the Treatment of Degenerated Mitral Bioprostheses. J Cardiol,131:99−103.	Retrospective case series N=26 high-risk patients with previous surgical mitral valve replacement or repair with annular ring that underwent TMVI (20 had prior surgical mitral valve replacement and 6 had prior repair with annular ring) Follow-up 1 year	Early experience with treatment of degenerated mitral bioprostheses using TMVI in high-risk patients resulted in significant short-term and sustained long-term improvements in mean mitral gradient, MR and heart failure symptoms.	Larger studies included in table 2.
Mick SL, Roselli EE, Kapadia S et al. (2016) Postoperative migration of an Edwards-SAPIEN XT mitral valve-in-valve treated with direct vision implantation during beating-heart bypass. Ann Thorac Surg; 101:1182–5	Case report N=1 Transapical mitral transcatheter valve-in-valve (TAMVI) implantation into a failed mitral bioprosthesis	Migration of a transcatheter balloon-expandable Edwards-SAPIEN XT valve within a previously implanted surgical Carpentier-Edwards valve was reported. This was treated with direct-vision valve-in-valve implantation with a balloon-expandable prosthesis.	Safety event already reported in systematic reviews added to table 2.

Nachum ER, Raanani E, Segev A et al. (2016) Transapical transcatheter valve-in-valve implantation for failed mitral valve bioprosthesis. IMAJ, 18, 13-17.	Case series N=10 transapical VIV implantation for failed bioprosthesis (mitral 9, aortic 1) Follow-up mean 13 months.	Successful implantation in all and no in-hospital mortality or major complications. Femoral access bleeding in 1. Hospital stay was 15 days. All alive and in NYHA class I or II. Mitral regurgitation was mild in 2. Peak and mean gradients changed from 26 and 8 at baseline to 16 and 7.	Larger and longer follow-up studies included in table 2.
Nez JC, Uribarri A, Martn A et al. (2018) Repeat fibrinolysis to treat thrombotic dysfunction of a mitral valve-in-valve prosthesis. Revista espaola de cardiologa. 71, 2, 117-118.	Case report N=1 transcatheter implantation - valve-in-valve to treat mitral prosthesis dysfunction with severe regurgitation.	Suspected mitral thrombosis, showed a thrombus within the prosthetic valve causing a severe obstruction. This was treated with fibrinolysis.	Safety event already reported in systematic reviews added to table 2.
Quick S, Speiser U, Strasser RH, Ibrahim K (2014). First bioprosthesis thrombosis after transcatheter mitral valve-in-valve implantation: diagnosis and treatment. J Am Coll Cardiol. 63: e49.	Case report 1 patient had transcatheter mitral valve-in-valve implantation. Follow-up 3 months	3 months after procedure, severe mitral valve stenosis with unusual leaflet thickening noted. After antithrombotic treatment, a significant decrease in transvalvular gradient and significant regression of the leaflets thickening was observed. This confirmed the diagnosis of bioprosthesis thrombosis.	Safety event already reported in studies added to table 2.

Ranney DN, Williams JB, Wang A, et al. (2016) Valve-in-Valve Transcatheter Valve Implantation in the Nonaortic Position. J Card Surg; 31:282-8.	Case series N=5 patients (4 with bioprosthetic mitral valve dysfunction and one for bioprosthetic tricuspid valve dysfunction) had ViV implantation. Mean follow-up of 21 months	No deaths occurred. NYHA class decreased from class IV at baseline to class I or II for all patients. No paravalvular leaks greater than trivial were encountered. Median mean gradient after mitral replacement was 6.5 mmHg and following tricuspid replacement was 4 mmHg. Post-operative complications included haematuria, epistaxis, acute kidney injury, and atrial fibrillation.	Larger and longer follow-up studies included in table 2.
Raval J, Nagaraja V et al (2014). Transcatheter valve-in-valve implantation: a systematic review of literature. Heart, Lung & Circulation 23 (11) 1020-1028.	Systematic review overview of valve-in-valve implantation using transcatheter heart valves (THVs) in aortic, mitral, pulmonary, tricuspid positions.	61 studies were included the review. This included 31 studies reporting transcatheter aortic valve-in-valve implantation, mitral valve-in-valve implantation (13 studies), tricuspid valve-in-valve implantation (12 studies), and pure native aortic valve regurgitation (9 studies). Limitation of this review is that most of the studies included were case reports, together with some case series. Valve-in-valve implantation can be an alternative to open heart	Overview of valve-in-valve implantation using transcatheter heart valves (THVs) in aortic, mitral, pulmonary, tricuspid positions. Narrative summary.

		surgery for high-risk patients. Large cohort studies or randomised trials with long-term follow-up are necessary.	
Seiffert M Conradi Let al (2012). Transcatheter mitral valve-in-valve implantation in patients with degenerated bioprostheses. Jacc: Cardiovascular Interventions 5 (3) 341-9.	Prospective case series n=6 patients with deteriorated mitral valve bioprosthesis and considered high risk for surgical valve replacement had transapical transcatheter mitral valve-in-valve implantation. Follow-up mean 70 days.	Implantation was successful in all with reduction of mean transvalvular gradients from 11.3 mm Hg to 5.5 mm Hg (p = 0.016) and median regurgitation from grade 3 to 0 (p = 0.033) with trace paravalvular regurgitation remaining in 2 patients. Apical bleeding occurred in 2 patients requiring intervention and 1 of them died 6 days later. Median NHYA class improved from 3.0 to 2.0 (p = 0.048).	Larger and longer follow-up studies included in table 2.
Sarkar K, Reardon MJ, Little SH et al. (2017) Transcatheter Mitral Valve Replacement for Native and Failed Bioprosthetic Mitral Valves. Methodist Debakey Cardiovascular J, 13 (3) 142-151	Review	Review highlights the current nascent state of TMVR and summarizes relevant insights from the limited contemporary experience with this procedure in three patient cohorts: those with severe degenerative or functional MR, failed mitral bioprostheses or repair, and DMS.	Review
Schaefer U, Conradi L, Lubos E,	Case report	Patient was successfully treated	Larger and longer follow-up studies

et al. (2016) First-in-man treatment of a degenerated mitral surgical valve with the mechanical expanding Lotus valve. EuroIntervention; 12:515-8.	N=1 patient (log EuroSCORE 22.9%) with a degenerated biological mitral prosthesis treated by transapical implantation of a Lotus valve.	with a mechanically expanding Lotus valve.	included in table 2.
Schaefer U, Conradi L, Lubos E, et al. (2015) First-in-man treatment of the mechanical expanding Lotus valve in degenerated surgical valves in mitral position. Catheterization and Cardiovascular Interventions 86:1280–1286	Case series N=3 patients with a degenerated mitral bioprosthesis were treated by transapical implantation of the LotusVR valve.	Procedural success was 100%. Valvular mitral regurgitation was eliminated in all patients. One patient had a mild paravalvular leak of the surgical bioprosthesis. Stable hemodynamics throughout the procedure offers a new and valuable treatment option.	Larger and longer follow-up studies included in table 2.
Tomi A, Meindert P, Versteegh MIM et al. (2016). Prosthesis dislocation after transapical valve-in-valve mitral valve implantation. Canadian journal of cardiology, 32 (12): 1576.e7-1576.e9	Case report N=1 Transapical valve-in-valve mitral valve implantation (TA-MVI) in patients with degenerated bioprostheses in the mitral position.	Prosthesis dislocation and migration into the left atrium after TA-MVI was reported. A new prosthesis was implanted using the same approach. The dislocated prosthesis was successfully removed through the left atrial appendage through an extended anterolateral thoracotomy without the use of cardiopulmonary bypass.	Safety event already reported in systematic reviews added to table 2.
Webb JG, Wood DA, Ye J et al. (2010) Transcatheter	Case series N=24 high risk patients with failed valves (aortic,	Procedure success 75% in mitral VIV implantations, survival at 30 days	Larger and longer follow-up studies included in table 2.

valve-in-valve implantation for failed bioprosthetic heart valves. Circulation 121: 1848–57.	mitral, pulmonary, tricuspid) **7** patients with deteriorated mitral valve bioprosthesis had transapical mitral VIV implantation. Transapical (in 5), transseptal (in 1) and transatrial (in 1). Follow-up mean 93 days.	and 72 days was 86% and 71%. 88% of patients were in class I or II. Echocardiographic outcomes improved. 2 patients died within 30 days.	Study also included data on VIV implantations in other positions (aortic, pulmonary, tricuspid).
Wilbring M, Alexiou K et al (2013). Transapical transcatheter valve-in-valve implantation for deteriorated mitral valve bioprostheses. Annals of Thoracic Surgery 95 (1) 111-7.	Case series N=7 patients with deteriorated mitral valve bioprosthesis had transapical mitral VIV implantation. Follow-up mean 125 days.	Successful implantation in all. Postoperatively, excellent hemodynamics with no mitral regurgitation in 5 patients and minimal regurgitation in 2 patients. Transvalvular pressure gradients decreased significantly. One patient had fatal pneumonia on day 34. No patient died and all patients remained in NYHA class I or II.	Larger and longer follow-up studies included in table 2.
Yoon SH, Whisenant BK, Bleiziffer S, et al. (2017) Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annulo-plasty rings. J Am Coll Cardiol. 70:1121–1131	Case series (TMVR registry) N=248 TMVR in patients with failed mitral bioprosthetic valves (valve-in-valve [ViV=176]) and annuloplasty rings (valve-in-ring [ViR=72]).	Technical and device success rates were 92.3% and 85.5%. Compared with the ViV group, the ViR group had lower technical success (83.3% vs. 96.0%; p =0.001) due to more frequent second valve implantation (11.1%	Study included in systematic review added to table 2. A more recent study from the same author is also included in table 2.

		vs. 2.8%; p = 0.008), and lower device success (76.4% vs. 89.2%; p = 0.009) due to more frequent reintervention (16.7% vs. 7.4%; p = 0.03). Mean mitral valve gradients were similar between groups (6.4 mm Hg vs. 5.8 mm Hg; p = 0.17), whereas the ViR group had more frequent postprocedural mitral regurgitation (19.4% vs. 6.8%; p = 0.003). Furthermore, the ViR group had more frequent life-threatening bleeding (8.3% vs. 2.3%; p = 0.03), acute kidney injury (11.1% vs. 4.0%; p = 0.03), and subsequent lower procedural success (58.3% vs. 79.5%; p=0.001). The 1-year all-cause mortality rate was significantly higher in the ViR group compared with the ViV group (28.7% vs. 12.6%; log-rank test, p = 0.01). On multivariable analysis, failed annuloplasty ring was independently associated with all-cause mortality (hazard ratio: 2.70;	

		95% CI: 1.34 to 5.43; p = 0.005).	
Yoon SH, Beliziffer S, Latib A et al (2019) Predictors of Left Ventricular Outflow Tract Obstruction After Transcatheter Mitral Valve Replacement. JACC: Cardiovascular Interventions. 12 (2)182-93.	Registry analysis N=194 patients with pre-procedural multidetector row computed tomography MDCT undergoing TMVR for failed mitral bioprosthetic valves (valve-in-valve, 107 patients; valve-in-ring, 50 patients; valve-in-MAC, 37 patients),	LVOT obstruction was observed in 26 patients (13.4%), with a higher rate after valve-in-MAC than valve-in-ring and valve-in-valve (54.1% vs. 8.0% vs. 1.9%; p < 0.001). Patients with LVOT obstruction had significantly higher procedural mortality compared with those without LVOT obstruction (34.6% vs. 2.4%; p < 0.001). Receiver-operating characteristic curve analysis showed that an estimated neo-LVOT area ≤1.7 cm2 predicted LVOT obstruction with sensitivity of 96.2% and specificity of 92.3%.	Study to identify the predictors of LVOT obstruction. Outcomes reported in another study added to table 2.