NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transapical transcatheter mitral valve-in-ring implantation after failed annuloplasty for mitral valve repair

If the mitral valve in the heart leaks, an annuloplasty ring can be surgically implanted to tighten the mitral valve ring (annulus) so the valve leaflets close properly.

In this procedure, a tube (catheter) is passed through a cut in the chest wall and then through the heart wall (transapical) and positioned across the leaking mitral valve. A bioprosthetic mitral valve is then passed through the tube (transcatheter) and placed within the existing mitral valve ring. The aim is to treat the leaking mitral valve without needing to repeat open heart surgery.

Contents

Abbreviations

Word or phrase	Abbreviation
basal maximal gradient.	∆P
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 valve-in-mitral annular calcification	TVIMAC
Transapical	TA
Transeptal	TS
Society of Thoracic Surgeons	STS

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 August 2020 and updated in March 2021.

Procedure name

- Transapical transcatheter mitral valve-in-ring implantation after failed annuloplasty for mitral valve repair

Professional societies

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

Description of the procedure

Indications and current treatment

The mitral valve allows blood to flow from the left atrium to the left ventricle. Mitral valve regurgitation happens when the valve does not close properly and blood flows back into the atrium from the ventricle. The heart has to work harder to pump blood from the left ventricle to the aorta, resulting in an enlarged left ventricle. If not treated, this can lead to shortness of breath, fatigue and palpitations (because of atrial fibrillation) and eventually heart failure.

If symptoms of mitral valve regurgitation are severe enough, mitral valve annulus surgical repair may be done by open heart surgery in patients who are well enough for this kind of operation. A surgical valve annulus repair may fail over time and can result in the need for further intervention.

The standard treatment after a failed mitral valve annuloplasty is repeat open heart surgery. Repeat open heart surgery is associated with a higher risk of morbidity and mortality than primary surgery. Transapical transcatheter mitral valve-in-ring implantation is a less invasive alternative. It avoids the need for cardiopulmonary bypass and can be used to treat failed annuloplasty rings originally placed during open heart surgery.

What the procedure involves

The procedure is usually done with the patient under general anaesthesia and using imaging guidance including fluoroscopy, angiography and transoesophageal echocardiography. 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 mini thoracotomy (transapical approach). A guidewire is placed across the existing native mitral valve and into a pulmonary vein. A balloon catheter delivery system is then advanced over the guidewire into the left atrium. The inner diameter of the mitral valve annulus is measured using transoesophageal echocardiography to establish the size of bioprosthetic valve needed. Using the delivery system, the bioprosthetic valve is then introduced, manipulated into position (to align the valve with the mitral annulus) and slowly deployed within the surgically implanted mitral valve ring under fluoroscopic and echocardiographic 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 from the left ventricle 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 than1.0 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-ring implantation (TMVIR, in 73 patients) for failed annuloplasty rings or transcatheter mitral valve-in-valve implantation (TMVIV, in 172 patients) for degenerated mitral bioprosthetic valves, the overall technical success rate was 94% (229/245). The TMVIR procedure was associated with a lower technical success rate (85%, 62/73) than the TMVIV procedure (97%, 167/172, 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 (TMVIR TA 90%, [35/39] versus TS 87%, [26/30], p=0.427; TMVIV TA 99%, [93/94] versus TS 95%, [58/61], p=0.337). Patients in both groups with different mitral valve failure modes (mitral regurgitation [MR] or mitral stenosis [MS]) achieved a high technical success rate (TMVIR MR 86%, [37/43] versus MS 93%, [13/14]; p=0.837; TMVIV MR 94%, [50/53] versus MS 100% [35/35]; p=0.405). Thirteen technical failures happened in the TMVIR group (3 of them were because of partial ring dehiscence after prosthesis deployment, and 1 was related to incomplete ring expansion) and 5 happened in the TMVIV group (Hu 2018).

In a retrospective registry analysis of 1,079 patients (from the Valve-in-Valve International Data Registry) who had TMVIR for failed surgical repairs with annuloplasty rings (in 222 patients) and TMVIV implantation for degenerated mitral bioprosthetic valves (in 857 patients), the overall technical success rate was 91%. The TMVIR procedure was associated with lower technical success rate than TMVIV (TMVIR 82% versus TMVIV 94%; p<0.001). Technical success was defined as exit from catheterisation laboratory by the mitral valve academic research consortium (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; Simonato 2020).

In a retrospective registry analysis of 903 patients (from the Transcatheter Valve Therapy Registry) who had TMVIR for failed surgical repairs with annuloplasty rings (in 123 patients), TMVIV implantation for degenerated mitral bioprosthetic valves (in 680 patients), and transcatheter valve-in mitral annular calcification (TVIMAC, in 100 patients), the overall technical success rate was 88% (793/902). The TVIMAC procedure was associated with lower technical success rate followed by TMVIR and TMVIV (TVIMAC=74% [74/100]; TMVIR=83% [102/123], TMVIV=91% [617/679]; 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 re-intervention related to the device or access procedure; Guerrero 2020).

In a retrospective registry analysis of 521 patients (from the Transcatheter Mitral Valve Registry) with TMVIR for failed surgical repairs with annuloplasty rings (in141 patients), TMVIV implantation for degenerated mitral bioprosthetic valves (in 322 patients), and TMV for severe annular calcification (TVIMAC, in 58 patients), the overall technical success rate was 87% (454/521), with a lower success rate after TVIMAC followed by TMVIR and TMVIV (TVIMAC 62% [36/58], TMVIR 81% [114/141] and TMVIV 94% [304/322]; 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 (TMVIR 32% versus TMVIV 41%; 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 MR to either optimal or acceptable levels without significant MS (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), TMVIR still had lower rates of device success (TMVIR 63% versus TMVIV 84%; p<0.001). After excluding the hemodynamic component of the success definition (that is, residual stenosis or regurgitation), success rates were 82% in TMVIR and 94% in TMVIV (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 lower rate in TVIMAC group

followed by TMVIR and TMVIV groups (TVIMAC 88% [88/100], TMVIR 94% [115/123], and TMVIV 95% [646/680]; p<0.001). At 30 days follow up, overall device success rate was 79% (n=485), with a lower rate in TVIMAC group followed by TMVIR and TMVIV groups (TVIMAC=59% [n=41], TMVIR=68% [n=58], and TMVIV=84% [n=386]; 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 MR greater than 1 (Guerrero 2020).

The retrospective registry analysis of 521 patients reported that device success was lower in the TVIMAC group followed by TMVIR and TMVIV groups (TVIMAC 53% [31/58], TMVIR 70% [98/141] and TMVIV 85% [273/322]; 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 lower in TMVIR and TVIMAC groups and higher in TMVIV group (TMVIR 60% [n=50], TVIMAC 49% [n=36], and TMVIV 76% [n=359]; 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 lower in the TVIMAC group followed by the TMVIR and TMVIV groups (TVIMAC 41% [24/58] versus TMVIR 57% [81/141] versus TMVIV 74% [237/322]; p<0.001; Yoon 2019).

In a case series of 17 patients with high risk of redo surgery who had TMVIR for failed surgical ring annuloplasty, procedural success rate was 88% (15/17). Procedural success through a transapical approach was 89% (8/9) and through a transeptal approach was 87% (7/8). Procedural success was defined as delivery of the prosthesis in the correct position, without procedural complications (Descoutures 2013).

Symptomatic improvement

In the systematic review of 245 patients there was significant improvement in New York Heart Association (NYHA) functional class 3/4 after the procedure (overall, from baseline 98% [165/168] to 6% [7/113] post procedure, p<0.001,

TMVIR from baseline 100% [57/57] to 4% [1/39] post procedure, p<0.001 and TMVIV from baseline 97% [108/111] to 8% [6/74] post procedure, p<0.001). No significant differences were found in NHYA outcomes in those with different mitral valve access routes (TMVIR TA 100% [18/18]) versus TS 93% [14/15], p=0.455; TMVIV TA 94% [46/49] versus TS 100% [12/12]; p>0.999) and between patients who had different mode of failures (TMVIR MR 95% [18/19] versus MS 100% [9/9], p>0.999; TMVIV MR 94% [33/35] versus MS 100% [14/14]; 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% [801/894], TMVIV 91% [611/675], TMVIR 88% [105/120], TVIMAC 86% [85/99], p=0.155). At 30 days follow up, fewer patients were in NYHA functional class 3 or more (overall 18% [86/475], TMVIV 16% [57/362], TMVIR 18% [12/66], TVIMAC 36% [17/47]). Most patients were in NYHA class 1 or 2 (overall 82% [389/475], TMVIV 84% [305/362], TMVIR 82% [54/66], TVIMAC 64% [30/47], p=0.007; Guerrero 2020).

Transvalvular gradient

In the systematic review of 245 patients, the mean trans-mitral gradient after both procedures decreased significantly (TMVIR from 9.5 ± 5.2 mmHg [n=34] to 5.1 ± 2.5 mmHg [n=44], p<0.001; TMVIV from 12.8 ± 5.9 mmHg [n=121] to 5.1 ± 2.5 mmHg [n=96], p<0.001;). No statistically significant differences were found in those with different mitral valve access routes (TMVIR, TA 4.3 ± 2.3 [n=19] versus TS 5.9 ± 2.6 [n=21], p=0.071; TMVIV, TA 5.1 ± 3.1 [n=39] versus TS 5.4 ± 2.5 [n=43], p=0.652) and between patients who had different mode of failures (TMVIR, MR 4.2 ± 1.9 [n=21] versus MS 6.7 ± 2.4 [n=15], p=0.002; TMVIV, MR 5.6 ± 2.7 [n=45] versus MS 5.0 ± 3.2 [n=28], p=0.378; 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, TMVIR from 7.8 to 6.0 mmHg [p<0.001]; TMVIV from 11.4 to 5.6 mmHg [p<0.001]). At 1-year follow up, a slight but statistically significant increase was reported in the TMVIV group (6.7 mm Hg, 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 TMVIR and TMVIV groups and 6 mmHg in the TVIMAC group (p=0.014; Guerrero 2020).

Mitral valve area

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

Left ventricular ejection fraction (LVEF)

The retrospective registry of 1,079 patients reported that post-procedural LVEF decreased from baseline in both TMVIR and TMVIV 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 substantial post-procedure decreases in MR severity after both TMVIR and TMVIV 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).

Survival

In the retrospective registry analysis of 1,079 patients, 1-year survival was significantly lower in patients who had TMVIR than those who had TMVIV (77% versus 86%, p=0.004). At 4-years follow up, TMVIR patients had significantly lower survival than TMVIV patients (50% versus 62%, p=0.002). Patients at high risk for repeat open heart surgery (STS score ≥ 8%) also had significantly lower survival at 4-years follow up (TMVIR 54% versus TMVIV 67%, p<0.001; Simonato 2020).

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=0.958) and different access routes in the TMVIR procedures (TA or TS, p=0.361). Similarly, 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; Hu 2018).

In the case series of 17 patients at high risk of redo surgery who had TMVIR for failed surgical ring annuloplasty, 30-day survival was 82% (14/17) and at last follow up (13 ± 5 months) it was 71% (12/17; Descoutures 2013).

Safety summary

Death in-hospital

In the systematic review of 245 patients, mortality rates before discharge were 7% (5/73) and 5% (9/172) in the TMVIR and TMVIV groups respectively; 7% (5/73) and 3% (5/172) were cardiovascular related. No significant differences were found in death rate between patients who had different mode of failures (TMVIR, MR 7% [3/45] versus MS 0% [0/14], >0.999; TMVIV, MR 8% [3/39] versus MS 0% [0/24], p=0.404) and those with different mitral valve access routes (TMVIR, TA 10% [4/39] versus TS 3% [1/30], p=0.528); TMVIV, TA 3% [3/94] versus TS 7% [4/61], p>0.555) 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 higher in the TVIMAC group followed by TMVIR and TMVIV groups (TVIMAC 18% [18/100], TMVIR 9% [11/123] and TMVIV 6% [43/679]; p=0.004). The rate of cardiovascular related deaths was 5% (43/900) and non-cardiovascular related deaths was 3% (29/900; Guerrero, 2020).

Death within 30 days and 6 months

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

The retrospective analysis of 1,079 patients reported that 30-day mortality was 9% in the TMVIR group and 7% in the TMVIV 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 higher in TVIMAC group followed by TMVIR and TMVIV groups (TVIMAC 22% [n=20], TMVIR 12% [12/104], and TMVIV 8% [47/584]; 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 higher in the TVIMAC group followed by TMVIR and TMVIV groups (TVIMAC 34% [20/58], TMVIR 10% [14/141] and TMVIV 6% [20/322]; p<0.001; Yoon 2019).

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%, TMVIV 31% and TVIMAC 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).

Left Ventricular Outflow Tract (LVOT) obstruction

In the systematic review of 245 patients, LVOT obstruction happened more frequently during the procedure in patients who had TMVIR procedures than those who had TMVIV procedures (TMVIR 5% [4/73] versus TMVIV 0% [0/172]; 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 more frequent in patients who had TMVIR (TMVIR 6%, TMVIV 2%, 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 more frequent in patients who had TMVIR and TVIMAC (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 higher rate after

TVIMAC than TMVIR and TMVIV procedures (TVIMAC 40% [23], TMVIR 5% [7] and TMVIV 2% [7] p<0.001; Yoon 2019).

Valve migration

In the systematic review of 245 patients, valve migration in the TMVIR group was reported in 4% of patients at discharge (3/73) and at 30-day follow up (2/47). 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). In the TMVIV group, 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; Hu 2018).

In the retrospective analysis of 1,079 patients, significantly more patients who had TMVIR reported valve migration, malposition or embolisation during the procedure than those who had TMVIV (7% versus 2%; 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 embolisation during the procedure and at 30-day follow up were more common in patients who had TMVIR, 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 embolisation during the procedure were seen in 2% (9/521) of patients overall, and more frequently in patients who had TVIMAC 7% (4/58) than those who had TMVIR 1% (2/141) and TMVIV 0.9% (3/322; Yoon 2019).

Stroke

In the systematic review of 245 patients, strokes were reported before discharge in 1% (1/73) of patients who had TMVIV 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 in the TMVIR group between patients who had different mitral valve access routes (TA 3% [1/39] versus TS 0% [0/30], p>0.999). In the TMVIV group, strokes were reported before discharge in 2% (3/172) of TMVIV patients before discharge 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; Hu 2018).

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

In the retrospective analysis of 903 patients, ischemic stroke after the procedure and at 30-day 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).

Thrombosis

In the systematic review of 245 patients, thrombosis (on the ventricular aspect of the mitral bioprosthesis) was not reported in any patients in TMVIR group but was reported in 1 patient who had TMVIV before discharge and rates at 30 days and 6 months increased to 3% (3/95) and 8% (5/60) respectively (Hu 2018).

In the retrospective registry analysis of 903 patients, device thrombosis was not reported in any patients in TMVIR and TVIMAC groups but was reported in 1 patient in the TMVIV group (n=680) at 30-day follow up (Guerrero 2020).

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

Bleeding

In the systematic review of 245 patients, bleeding was not reported in any patients who had TMVIR but was reported in 9% (15/172) of patients who had TMVIV before discharge. These included 2 left ventricular apical perforations during the procedure and 13 access-site bleeding events after the procedure (Hu 2018).

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

The retrospective registry analysis of 903 patients reported no significant difference for major or 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).

Pseudoaneurysm

In the systematic review of 245 patients, pseudoaneurysm rates in patients who had TMVIR were less than 1% [1/47] before discharge, at 30-day follow up and 12% (1/8) at 6-months follow up. Pseudoaneurysm rates in patients who had TMVIV at 30 days and 6 months were 2% (2/95) and 4% (2/55) respectively (Hu 2018).

Device failure

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

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

Mitral valve re-intervention

In the retrospective registry analysis of 903 patients, mitral valve re-intervention during the procedure was significantly more common in patients who had TMVIR and TVIMAC than those who had TMVIV (overall 1% [11/902], TMVIV 3% [20/679], TMVIR 5% [6/123], TVIMAC 4% [4/100]; p=0.003). At 30-day follow up, it was also significantly more common in patients who had TVIMAC (overall, 1% [7], TMVIV 0.4 [2], TMVIR 1% [1], TVIMAC 6% [4]; p=0.002; Guerrero 2020).

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 or transcatheter mitral valve replacement (p=0.98) between the 3 groups (Yoon 2019).

Need for a second valve implantation

In the retrospective registry analysis of 1,079 patients, significantly more patients who had TMVIR needed a repeat transcatheter mitral valve replacement (MVR) than those who had TMVIV (10% versus 3%, p<0.001). The overall rate of repeat TMVR at 4 years was 3% (18 events: 13 open heart surgery, 5 transcatheter), with a higher rate in patients who had TMVIR (TMVIR 6% versus 2% TMVIV; p<0.001). There was no difference in the 4-year rate of repeat TMVR for patients with immediate post-procedural mean gradient of more than 5 mmHg (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 more than 10 mmHg (13% versus 2%; p<0.001). Both significant residual MS (sub hazard ratio [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 associated with a need for repeat MVR (Simonato 2020)

In the retrospective registry analysis of 903 patients, significantly more patients who had TVIMAC and TMVIR needed a second valve implantation during the procedure than those who had TMVIV (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 more frequently done in TMVIR group than TMVIV and TVIMAC groups (12% [17] versus 3% [8] versus 5% [3] p<0.001; Yoon 2019).

Unplanned or 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 more common in TMVIR and TVIMAC groups than TMVIV group (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 6% (4/73) of patients who had TMVIR before discharge. No significant differences were found

in AKI rates between patients with different mitral valve access routes (TMVIR TA 7% [3/39] versus TS 0% [0/30], p= 0.327; TMVIV TA 8% [8/94] versus TS 3% [2/61] p=0.337) and those who had different mode of failures (TMVIR MR 3% [1/29] versus MS 0% [1/10], p= 0.452; TMVIV MR 13% [5/39] versus MS 4% [1/24] p=0.4875; 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 more common in patients who had TMVIR and TVIMAC than those who had TMVIV (TMVIV 3% [n=19], TMVIR 6% [n=7], TVIMAC 8% [n=7]; p=0.034). At 30-day 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 TMVIR and TMVIV groups (TMVIR 13%, TMVIV 9%; p=0.07; Simonato 2020).

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

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 12% (8/67) of TMVIR 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). In the TMVIV group, MR was reported in 6% (8/145) of 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; Hu 2018).

The retrospective registry analysis of 1,079 patients reported that significant residual MS (defined as mean gradient 10 mmHg or more) happened in 12% of patients who had TMVIR and 8% of patients who had TMVIV (p=0.09) after the procedure and no significant association was found with survival at 4 years (60% versus 66%, p=0.89). Significant residual MR (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 MS were smaller true internal diameter, younger age and larger body mass index. The only correlate for significant residual MR

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 MR 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-day follow up, residual MR grade 2 or more was significantly more common in patients who had TMVIR and TVIMAC than those who had TMVIV (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 MR (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 trans-mitral 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 more frequently seen in the TMVIR group followed by TVIMAC and TMVIV groups (TMVIR 18% [n=26], TVIMAC 14% [n=8], TMVIV 6% [n=18]; p< 0.001). At 30-day follow up, the rates of MR remained higher in the TMVIR and TVIMAC groups compared with TMVIV group (TMVIR 13% [n=16],TVIMAC 13% [n=5] and TMVIV 3% [n=10] versus; p<0.001; Yoon 2019).

Cardiac arrest

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

Arrhythmia

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

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=33], TMVIV 2% [n=15], TMVIR 2% [n=3], TVIMAC 5% [n=5]; p=0.279; Guerrero 2020).

Vascular complications

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

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).

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

Conversion to surgery (including unplanned vascular surgery/interventions)

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

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; Guerrero2020).

In the case series of 17 patients at high risk of redo surgery who had TMVIR for failed surgical ring annuloplasty, emergency surgery was needed in 1 patient because of acute dislodgement of the ring after valve placement. Both ring and prostheses were removed, and a surgical mechanical valve prosthesis was implanted (Descoutures 2013).

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).

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 TMVIR and TMVIV groups (TMVIR 27%, TMVIV 24%; p=0.54; Simonato 2020).

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 ring implantation after failed annuloplasty for mitral valve repair. The following databases were searched, covering the period from their start to 09.03.2021: 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 mitral valve repair surgery.
Intervention/test	Transapical transcatheter mitral valve in ring 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 2,765 patients (576 patients with TMVIR, 2,031 patients with TMVIV, and 158 patients with TVIMAC) from 1 systematic review[1], 3 retrospective registry analyses[2-4], and 1 case series[5]. The case series was included in the systematic review.

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-ring implantation after failed annuloplasty for mitral valve repair

Evidence on TMVIR implantations presented in studies below[1,3-5] included data on both transapical and transseptal access routes. Approximately 53% of the procedures were done using the transapical access route and 47% 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 > 3 (%): 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 have 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 through a 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).

^^ p value between groups.

** 3 of them were because of partial ring dehiscence following prosthesis deployment, and 1 was related to incomplete ring expansion.

*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 ≥3l, %			
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 %	4.1 (10/245)	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)
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)

IP overview: Transapical transcatheter mitral valve in ring implantation after failed annuloplasty for mitral valve repair

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 due to 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 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 to 996 days].

	TMVIV group (519 days [IQR 95.5 to 1,007 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 1,211.75 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; Incomplete rings were present in 9.4% of VIR patients.

Other issues: Transapical access was used in most cases. Authors state there was also 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). They also state that 'there were significant shifts toward treating lower risk patients and increasingly using 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 haemolysis).

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

^^Considering only the components of device success not related to haemodynamics, that is procedural death, malposition/embolisation/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 four years (TMVIV 66.8% versus 54.1%, p<0.001).

There were no significant 4-year survival differences between TMVIR patients with semi-rigid rings and those with rigid/flexible rings (51.1% versus 47.3%, respectively; p=0.79) and also no differences between those with complete and incomplete rings (49.5% versus 56.1%, respectively; p=0.93). Rates of technical success (81.9% semi-rigid versus 82.7% rigid/flexible; p=0.89) and device success (29.4% semi-rigid versus 40.4% rigid/flexible; p=0.14) were similar between ring types.

Echocardiographic outcomes (at median 772.5 days, IQR 510 to 1211.75 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)	

Mitral regurgitation (MR)

	Overall % (n=1070)	**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 ≥ 10 mmHg or cardiogenic shock clinically related to a complication)	2.6	1.8	5.9	0.001
Malposition*/embolisation/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				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 >5 mmHg)	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	8.6	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 cm^2/m^2 for patients with body mass index (BMI) <30 kg/m^2 and indexed EOA ≤0.75 cm^2/m^2 for those with BMI ≥30 kg/m^2

^^ significant residual MR was associated with lower survival at 4 years (35.1% versus 61.6% no residual MR; p=0.02). No association was found for significant residual MS (66.1% versus 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 3 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 to 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 to 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.

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**	**TVIMAC**	**P value**
Ejection fraction (%)					
Baseline	55 (47–62.5) (n=885)	55 (49–62) (n=665)	50 (35–58) (n=122)	60 (55-65) (n=98)	<0.001
30 days	55 (45–60) (n=460)	55 (45-60) (n=355)	45 (33-58) (n=54)	58 (53-67) (n=51)	<0.001
Mean mitral valve gradient, mmHg					
Baseline	11 (7–16) (n=885)	12 (8–17) (n=665)	7 (5–12) (n=122)	11 (7.5–13.5) (n=98)	<0.001
Post procedure	4 (2–5) (n=829)	4 (3-5) (n=632)	4 (2-5) (n=110)	4 (2-6) (n=87)	0.862
30 days	7 (5–9) (n=450)	7 (6-9) (n=348)	7 (6-9) (n=53)	6 (4-8) (n=49)	0.014
Mitral valve area, cm^2					
Baseline	1.3 (0.9–2.1) (n=885)	1.2 (0.8-1.9) (n=665)	1.8 (1.2-2.5) (n=122)	1.5 (1-2.5) (n=98)	<0.001
30 days	1.7 (1.4–2.3) (n=319)	1.7 (1.3-2.2) (n=249)	1.9 (1.5-2.4) (n=42)	1.9 (1.4-2.5) (n=28)	0.154

NYHA functional class

	Overall % (n=903)	TMVIV % (n=680)	TMVIR % (n=123)	TVIMAC % (n=100)	P value
Baseline					**0.155**
1	1.6 (14/894)	1.3 (9/675)	0.8 (1/120)	4 (4/99)	
2	8.8 (79/894)	8.1 (55/675)	11.7 (14/120)	10.1 (10/99)	
3	55.1 (493/894)	54.4 (367/675)	55.8 (67/120)	59.6 (59/99)	
4	34.5 (308/894)	36.1 (244/675)	31.7 (38/120)	26.3 (26/99)	
30 days					**0.007**
1	37.1 (176/475)	40.3 (146/362)	30.3 (20/66)	21.3 (10/47)	
2	44.8 (213/475)	43.9 (159/362)	51.5 (34/66)	42.6 (20/47)	
3	15.6 (74/475)	13.8 (50/362)	(16.7 (11/66)	27.7 (13/47)	
4	2.5 (12/475)	1.9 (7/362)	1.5 (1/66)	8.5 (4/47)	

Mitral regurgitation (MR)

	Overall % (n=903)	TMVIV % (n=680)	TMVIR % (n=123)	TVIMAC % (n=100)	P value
Baseline					**<0.001**
None/trace	17.6 (93/829)	20.4 (137/671)	6.5 (8/123)	12.2 (12/99)	
Grade 1	19.5 (174/829)	20.1 (135/671)	11.4 (14/123)	25.3 (25/99)	
2	14.4 (129/829)	13.9 (93/671)	15.4 (19/123)	17.2 (17/99)	
3 to 4	48.5 (433/829)	45.6 (306/671)	66.7 (82/123)	45.5 (45/99)	
Residual MR post procedure					**<0.001**
None/trace	75.1 (675/898)	42.5 (557/675)	51.2 (63/123)	55 (55/98)	
Grade 1	19.3 (173/898)	13.8 (93/675)	35.8 (44/123)	36 (36/98)	
2	4.1 (37/898)	2.5 (17/675)	10.6 (13/123)	7 (7/98)	
3 to 4	1.4 (13/898)	1.1 (8/675)	2.4 (3/123)	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 to 4	3.3 (15/458)	1.9 (7/352)	9.3 (5/54)	5.7 (3/352)	

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 (79/777)	8.1 (47/584)	11.5 (12/104)	21.8 (20/92)	0.003
Cardiovascular related	5.9 (46/777)	4.8 (28/584)	6.7 (7/104)	12 (11/92)	
Non-cardiovascular related	4.2 (33/777)	3.3 (19/584)	4.8 (5/104)	9.8 (9/92)	
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 4 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 conducted 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)

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	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)**	**TVIMAC (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 mmHg (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 mmHg	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)**	**TVIMAC % (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 >10 mmHg 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)	TVIMAC % (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 to 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 to 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% versus 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% versus 21.4%; log rank p=0.01).					

Study 5 Descoutures F

Study details

Study type	Case series
Country	Europe (6 centres)
Recruitment period	2010 to 2012
Study population and number	N=17 patients with failed mitral valve repair and high risk of redo surgery had TMVIR procedure Aetiology of mitral valve disease: functional in 9, rheumatic in 3, degenerative in 2, post-endocarditis in 1, post-irradiation in 1 and iatrogenic in 1. Mode of failure: regurgitation n=12; stenosis n=5 Mean time between surgery and repair failure: 7 ± 3 years NYHA function class 3 to 4: 100% Mean logistic EuroSCORE: 36 ± 17% STS-PROM score 13 ± 9%.
Age	Mean 70 ± 16 years.
Patient selection criteria	Patients who had severe symptomatic surgical mitral repair failure and were treated with TVIR via either the transseptal or the transapical approach, using the Edwards SAPIEN XT transcatheter heart valve.
Technique	TVIR procedure Prosthesis type: Edwards SAPIEN XT Prosthesis diameter: 26 mm in 15 patients, 23 mm and 29 mm in 1. Access route: transvenous transseptal (n = 8), or a transapical approach (n = 9). Annuloplasty rings: semi-rigid in 14 cases, flexible in 2, and rigid in 1. Annuloplasty Ring diameter: 26 mm in 4 patients, 27 mm in 1, 28 mm in 9, 30 mm, 31 mm and 34 mm in 1.
Follow-up	mean follow-up duration 13 ± 5 months.
Conflict of interest/source of funding	Authors were either consultants, proctors or received royalties from Edwards LifeSciences.

Analysis

Follow-up issues: limited follow up; 1 patient was lost to follow up.

Study design issues: multicentre study with small number of patients; data were collected by phone calls. Clinical outcome definitions were standardised definitions from the Valve Academic Research Consortium. Valve function was assessed according to American Society of Echocardiography/American College of Cardiology recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound.

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Key efficacy findings

- Number of patients analysed: 17

Clinical outcomes

Mean hospital stay	10 ± 4 days (range 3–26).
Overall procedural success rate (defined by delivery of the prosthesis in the correct position, without procedural complications) % (n)	88% (15/17)
Procedural success -transapical approach, % (n)	89% (8/9)
Procedural success-transeptal approach, % (n)	87% (7/8)
Baseline mean valvular gradient	13.4 mmHg
Final mean valvular gradient	7 ± 3 mmHg
Baseline mean valve area (cm^2)	1.1±0.3 cm^2
Final mean valve area (cm^2)	range 1.3 to 2.6 cm^2
NYHA class 2	100%
30-day survival	82% (14/17)
Survival at last follow-up (mean 13 months)	71% (12/17)
Paravalvular mitral regurgitation (none/mild)	100%

Key safety findings

	% (n)
Early post-operative deaths (due to refractory congestive heart failure on day 14 and 26)	2
Deaths after discharge (due to sepsis at 1-month, sudden unexplained death at 5 months, refractory heart failure at 7 months)	3
Emergency conversion to surgery (because of acute ring detachment after valve insertion and severe MR; ring and prostheses were removed, and a surgical mechanical valve prosthesis was implanted).	n=1
Second valve implantation in-first valve (because valve was implanted in an atrial position)	n=1
Interatrial shunt (left to right, septum closure device placed)	n=1
Valve dysfunction	0
Haemolysis	0

Validity and generalisability of the studies

- There are no randomised controlled studies or comparative studies comparing transapical TMVIR with current standard (surgical mitral valve replacement).
- Evidence on transapical TMVIR implantation is mainly from published observational studies and retrospective registry analyses.
- Around 36 to 60% of patients included in registry analyses had TMVIR implantations via transapical access and 35 to 50% had transseptal access (Simonato, 2020, Guerrero 2020, Yoon 2019).
- Evidence has been stratified and presented according to access routes in 1 systematic review (Hu 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 primary studies added to the systematic review. In total, 302 centres in Europe and North America contributed their valve-in-ring 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 ring implantation after failed annuloplasty for mitral valve repair were submitted.

Patient commentators' opinions

NICE's Public Involvement Programme sought patient commentary for this procedure but none was received.

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

- 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.

References

1. Hu J, Chen Y, Cheng S et al. (2018) Transcatheter mitral valve implantation for degenerated mitral bioprostheses or failed surgical annuloplasty rings: A systematic review and meta-analysis. J Card Surg; 33:508–519.
2. 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
3. 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.
4. 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.
5. Descoutures F, Himberta D, Maisanob F et al. (2013) Transcatheter valve-in-ring implantation after failure of surgical mitral repair. European Journal of Cardio-Thoracic Surgery 44 (2013) e8–e15.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	09/03/2021	Issue 3 of 12, March 2021
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	09/03/2021	Issue 3 of 12, March 2021
International HTA database (INAHTA)	09/03/2021	-
MEDLINE (Ovid)	09/03/2021	1946 to March 08, 2021
MEDLINE In-Process (Ovid)	09/03/2021	March 08,2021
MEDLINE Epubs ahead of print (Ovid)	09/03/2021	March 08, 2021
EMBASE (Ovid)	09/03/2021	1974 to 2021 March 08

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

The MEDLINE search strategy was translated for use in the other sources.

Strategy used:
1 (TMVIR or TMVIV or TMVR or TVIR or TMVI or TAVI or THV).tw.
2 Transcatheter Aortic Valve Replacement/
3 (transcathet* adj4 (mitral* or aortic* or cardiac* or bicuspid*or valv* or heart valv*) adj4 (replace* or implant* or repair* or procedur*)).tw. (8070)
4 or/1-3
5 Heart Valve Prosthesis/
6 Heart Valve Prosthesis Implantation/
7 ((heart* or mitral* or cardiac*) adj4 valve* adj4 (annulop* or bioprosth* or ring* or transapcia* or transsept* or transatrial* or prosthes* or implant* or replace*)).tw.
8 Bioprosthesis/
9 bioprosth*.tw.
10 valve in valve.tw.
11 valve in ring.tw.
12 cardiac valve annuloplasty/ or mitral valve annuloplasty/
13 or/5-12
14 4 and 13

15 mitral valve insufficiency/ or mitral valve stenosis/
16 (mitral valve* adj4 (insuffic* or regurgitat* or incomplete* or incompet* or stenosis* or detoriat* or dysfunct*)).tw.
17 or/14-16
18 Fail* mitral valve repair.tw.
19 Redo Mitral Valve Replace*.tw.
20 Redo Mitral Valve Repair*.tw.
21 Prosthesis Failure/
22 ((prosthes* or valve*) adj4 (fail* or malfunct* or dysfunct* or loosen* or complicat*)).tw.
23 or/18-22
24 17 and 23
25 Edwards SAPIEN THV.tw.
26 Tendyne Mitral Valve System.tw.
27 Twelve Intrepid Transcatheter Mitral Valve Replacement System.tw.
28 Edwards SAPIEN XT.tw.
29 carpentier-edwards prosthesis.tw.
30 or/25-29
31 4 or 30
32 24 and 31
33 Animals/ not Humans/
34 32 not 33
35 limit 34 to english language
36 limit 35 to ed=20200901-20210331

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
Attizzani GF, Cheung Tam C, and Markovitz A (2016) Transcatheter Mitral Valve-in-Ring Implantation in Prohibitive Surgical Risk Patients: Single Center Initial Experience in the	Case report N=2 patients with mitral valve repair failure and high surgical risk had	Post deployment TEE showed no mitral regurgitation (MR) and mean	Larger studies with longer follow-up added to table 2.

United States. Catheterization and Cardiovascular Interventions 88: E233–E238	**transapical** transcatheter mitral valve-in-ring (TMVIR) implantation with Sapien XT valve	gradient of 4.8 mm Hg. Patients recovered uneventfully and were discharged. At 4-month follow-up symptoms improved to functional status NYHA class 2.	
Allende R, Doyle D, Urena M et al. (2015) Transcatheter Mitral "Valve-in-Ring" Implantation: A Word of Caution. The Annals of Thoracic Surgery. 99 (4), pages 1439-1442.	Case report N=1 failed mitral valve repair in a dysfunctional mitral homograft had TMVIR procedure.		Larger studies with longer follow-up added to table 2.
Beytullah C, Sinem C, Gunes HM et al. (2021) Failed transcatheter mitral valve-in-ring implantation followed by transapical valve-in-valve within the ring and ad hoc paravalvular leak closure. Anatol J Cardiol; 25 (1): 50-53. DOI: 10.14744/AnatolJCardiol.2020.59163	Case report provides description of simultaneous transapical valve-in-valve implantation and the closure of severe PVL after a failed transseptal valve-in-ring procedure.	Transseptal approach might preclude the optimal placement of TMVIR. The currently available occluder and delivery systems are suboptimal and dedicated ones; therefore, a steerable system is needed for the prevention of malalignment. Transapical implantation enables a better control over the implant position and	Larger studies included in table 2.

		facilitates defect closure.	
Bouleti C, Fassa A-A, Himbert D et al. (2015) Transfemoral implantation of transcatheter heart valves after deterioration of mitral bioprosthesis or previous ring annuloplasty. JACC Cardiovasc Interv. 8(1 Pt A):83-91.	Case series N=17 patients for degenerated mitral bioprosthesis or previous ring annuloplasty (6 bioprostheses, **11 ring annuloplasties**) had **transfemoral implantation** of Edwards Sapien prosthesis Mean follow-up 22 months	Procedure was successful in 14 patients (82%). 2 complications occurred during rescue procedures (1 procedural death and 1 valve migration). Residual regurgitation was trace or less in 11 patients (69%) and mild in 4 patients (25%). Mean gradient decreased from 12 Hg to 8 mm Hg. During a mean follow-up of 22 months, 4 patients died, 3 from cardiac cause. The 18-month survival was 68% in the overall population and 78% for patients with elective procedure. One patient underwent mitral valve replacement due to periprosthetic mitral regurgitation. At last follow-up, 12 patients	Outcomes were not reported separately for TMVIR procedures.

		were in NYHA class ≤2 (75%) and 4 in class 3 (25%).	
Cannata S, Pasta S, Turrisi M et al. (2020) Predicting LVOT Obstruction in Transcatheter Mitral Valve Replacement for Failed Surgical Annuloplasty. Structural Heart, 4 (2)			Abstract not available.
Cheung A, Denti P, Kiaii B et al. (2017) Mitral Valve-in-Ring Implantation with a Dedicated Transcatheter Mitral Valve Replacement System. JACC: Cardiovascular Interventions. 10 (9), pages 2012-2014	Case report N=3 TMVIR cases using Tiara **transapical mitral implantation** (TMVIR) system to treat failed mitral valve repair with annuloplasty rings. Follow up: 30 days.	Uneventful TMVIR implantation in all. All patients were discharged with marked symptomatic improvement at 30-day follow-up and no complications.	Larger studies with longer follow-up added to table 2.
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
Coylewright M, Cabalka AK et al (2015). Percutaneous mitral valve replacement using a transvenous, transseptal	case series n=4 Patients at high risk of	The mean age was 72 +/- 9.9 years, and the average	Venous access out of remit.

approach: transvenous mitral valve replacement. Jacc: Cardiovascular Interventions 8 (6) 850-857.	reoperation with degenerative mitral prostheses (bioprosthetic valves or rings) who had **transvenous, transseptal mitral valve replacement**.	Society of Thoracic Surgeons risk score was 12.5 +/- 7.2%. All patients had severe, life-limiting dyspnoea. The 4 procedures were successful without intra- or post-procedural complications; echocardiography indicated a well-seated and functioning mitral valve-in-valve or valve-in-ring. Patients were discharged within 2 days after valve replacement with marked improvement in dyspnoea.	
Dahle G, Fiane, AE, Rein, K A. (2012) Transapical 29-mm Edwards SAPIEN-XT Aortic Valve in a 34-mm Mitral Annuloplasty Ring. Innovations: technology and techniques in cardiothoracic and vascular surgery. 7 (4), 290-94.	Case report A 71-year old with failed mitral valve repair had **transapical TMVIR** procedure with Sapien XT valve.	Valve deployment was successful, fitted well and turned out circular with good coaptation of the leaflets. Additional leads for cardiac resynchronization was placed.	Larger studies with longer follow-up added to table 2.
Dahle G, Rein K-A, Jonsson AL. (2013) Transapical Valve-in-Valve-in-Ring for Stenotic Mitral	Case report 53-year old woman -with failed mitral valve	The stenosis and regurgitation were	Larger studies with longer follow-

Valve Repair. Innovations 8 (5), 376-80.	repair (annuloplasty ring) and stenosis and at high risk of surgery had transapical valve-in-valve in-Ring implantation with Sapien XT valves. (i.e. 2 valves in one annuloplasty ring).	eliminated. Echocardiogram showed a mean gradient of 5 mm Hg, no regurgitation, and no obstruction in the LVOT. The patient was in a stable hemodynamic situation and was mobilized. Unfortunately, developed septicaemia and died 23 days postoperatively.	up added to table 2.
Eleid MF, Cabalka AK, Williams MR et al. (2016) Percutaneous Transvenous Transseptal Transcatheter Valve Implantation in Failed Bioprosthetic Mitral Valves, Ring Annuloplasty, and Severe Mitral Annular Calcification. JACC: Cardiovascular Interventions, 9 (11), Pages 1161-1174.	Case series N=48 **Percutaneous transfemoral antegrade transseptal implantation** of SAPIEN prosthesis was performed in 48 patients with degenerated mitral bioprosthesis (n = 33), previous ring annuloplasty (n = 9), and severe MAC (n = 6).	Acute procedural success was achieved in 88% (42/48) patients. Success rate of 73% (11/15) was achieved in patients with failed annuloplasty rings and MAC and 94% (31/33) in patients with degenerated mitral bioprosthesis. No patients had > mild residual mitral regurgitation; mean transvalvular gradients were 6 mm Hg. 30-	Venous access mainly.

		day survival was 85% in the overall group and 91% in the failed bioprosthetic mitral valve subgroup.	
Eleid MF, Wishenant BK, Cabalka AK, et al. (2017) Early outcomes of percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. JACC: Cardiovascular Interventions, 10 (19), Pages 1932-42.	Case series N=87 **Percutaneous transseptal implantation** of balloon-expandable transcatheter heart valves was performed in 87 patients with degenerated mitral bioprostheses (valve in valve [VIV]) (n= 60), previous ring annuloplasty (valve in ring) (n=15), and severe MAC (valve in MAC) (n=12). Follow-up 1 year	Overall acute procedural success was 90% (78/87) and 97% (58/60) in the VIV group, 74% (20/27) in the valve in ring/valve in MAC group. 30 day survival free of death and cardiovascular surgery was 95% (95% confidence interval [CI]: 92% to 97%) in the VIV subgroup and 78% (95% CI: 70% to 86%) in the valve in ring/valve in MAC group (p=0.008). 1-year survival free of death and cardiovascular surgery was 86% (95% CI: 81% to 91%) in the VIV group compared with 68% (95% CI: 58% to 78%)	Larger studies with longer follow-up added to table 2. Venous access mainly.

		(p=0.008). At 1 year, 90% (36/40) had NYHA functional class 1 or 2 symptoms, no more than mild residual regurgitation, and mean transvalvular gradient was 7 mm Hg.	
Frerker C, Kuck KH (2016) Transcatheter implantation of aortic valve prostheses into degenerated mitral valve bioprostheses and failed annuloplasty rings: outcomes according to access. EuroIntervention:12 (12): 1520-26	Case series N=24 patients underwent TMVIV (n=14) or TMVIR (n=10) for mitral regurgitation (MR; n=17) or stenosis (n=7) using balloon-expandable bioprostheses. Transapical (TA) access was chosen in 13, and **transseptal (TS) access in 11 patients.**	MVARC technical success, device success and procedural success were 95.8%, 41.7% and 33.3%, respectively, with no differences between access routes. Cardiac output increased significantly by 1.1±0.8 l/min in TS patients, but not in TA patients (ΔCO=0.0±0.5 l/min; p=0.0051). Overall, 3-year survival was 57.6% (95% CI: 33.9-81.3; TA 35.5% [5.2-65.9]; TS 90.9% [73.9-100]). Survival up to 4 years showed a clear	Outcomes not reported separately for TMVIV and TMVIR procedures.

		benefit in patients treated transeptally (p=0.045).	
Flynn CD, Wilson-Smith AR, Yan TD. (2018) Novel mitral valve technologies -transcatheter mitral valve implantation: a systematic review. Ann Cardiothoracic 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. VIV (N=44 in 8 studies) transapical in 90% VIR (n=20) Follow-up =197 days.	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 salvage an embolized prosthesis, who later died.	Native valve and bioprosthetic failures were treated with VIV and VIR implantations. More comprehensive and updated systematic reviews were included in table 2.
Fuchs A, Urena M, Chong-Nguyen C et al. (2020) Valve-in-Valve and Valve-in-Ring Transcatheter Mitral Valve Implantation in Young Women Contemplating Pregnancy. Circulation: Cardiovascular Interventions; 387-394	Case series N=12 young women contemplating pregnancy underwent transseptal valve-in-valve or valve-in-ring TMVI using the Edwards SAPIEN XT/3 valves (Bioprosthesis degeneration- 7 and	In young women, transseptal TMVI to treat failing bioprostheses may result in good short-term outcomes that allow uneventful pregnancies. The results are less favourable in women with failed	Larger studies included in table 2.

	annuloplasty failure- 5) Follow-up 1 year.	annuloplasty rings.	
Grover FL, Vemulapalli S, Carroll JD, et al. (2017) STS/ACC TVT registry. 2016 Annual Report of the Society of Thoracic Surgeons/American college of cardiology transcatheter valve therapy registry. J Am Coll Cardiol. 69:1215–1230.	TVT registry analysis N=344 patients at high risk of surgery had mitral valve replacement. TMVIV 262 versus TMVIR 82	The observed hospital mortality was 7.2%, and 30-day post-procedure mortality was 8.5%.	Updated TVT registry data added to table 2.
Hammerstring C, Sinning JM, Schiller W et al. (2013) Percutaneous implantation of a 26 mm Edwards SAPIEN-XT aortic valve prosthesis in a degenerated 30 mm mitral annuloplasty ring. European heart journal, 34 (23) pg. 1748	Case report 80-year old with a degenerated mitral annuloplasty ring and at high risk of surgery had a TMVIR implantation via a **transvenous, transseptal antegrade approach.**	Bioprosthesis was deployed successfully. Proper positioning and function of the bioprosthesis with reduced transvalvular pressure gradient, improved functional NYHA class 2 and no periprosthetic leakage was noted at discharge.	Larger studies included in table 2.
Himbert D, Brochet E, Radu C et al. (2011) Transseptal Implantation of a Transcatheter Heart Valve in a Mitral Annuloplasty Ring to Treat Mitral Repair Failure. Circulation: Cardiovascular Interventions. 4:396–398.	Case report 56-year old man with mitral valve repair failure and at risk of surgery had TMVIR through the right femoral vein and a **transseptal**	After implantation, trivial periprosthetic leak and a mean transmitral gradient of 8 mm Hg was noted, and	Larger studies with longer follow-up included in table 2.

	route using Sapien XT valve.	functional status improved. At 30-day follow-up, a stable functional status was reported.	
Jagielak D, Ciecwierz D, Fijalkowska J (2018) The Rare Complication of Transcatheter Mitral Valve-in-Ring Procedure: Not Only Left Ventricular Outflow Tract Obstruction Counts. JACC: Cardiovascular Interventions. 11 (19), Pages 2007-2008.	Case report 74-year-old man had TMVIR (with Sapien 3 valve) for failed mitral valve repair (annuloplasty ring and edge-to-edge commissural stitch).	After TMVIR implantation, severe central mitral regurgitation secondary to a prolapsing native anterior leaflet through the prosthesis into the S3 and mild paravalvular leaks were noted. After a few weeks, the anterior prolapsing mitral leaflet was removed by an aortic approach. The patient subsequently improved and has remained asymptomatic.	Larger studies included in table 2.
Kofler M, Unbehaun A, Klein C (2019) Transcatheter Valve-in-Valve and Valve in- Ring Interventions for Failing Bioprostheses and Annuloplasty Rings. Surgical technology international. 34, 313-320.	Review focuses on patient selection, procedure specific risk factors, technical aspects of VIV/VIR interventions, and explores	VIV/R is a valuable treatment option for patients for whom surgical reoperation is not possible. Procedural success is encouraging	Review

	literature on post intervention outcomes.	but further studies are needed to define the true value of these interventions in terms of long-term outcomes.	
Latib A, Ruparelia, N, Bijuklic K et al. (2016) First-in-man transcatheter mitral valve-in ring implantation with a repositionable and retrievable aortic valve prosthesis	Case series N=8 patients who underwent transcatheter mitral **valve-in-ring (VIR) implantation** of a DFM valve for failed mitral annuloplasty deemed high risk for redo surgery.	Successful implantation in all. Two required retrieval of the device due to a suboptimal result, and a further patient required repositioning of the valve with an ultimately successful implantation. During the 30-day follow-up period, 2 patients died for reasons unrelated to the valve implantation. The 4 patients with successful implantation had normal valve function associated with a significant improvement in their functional status.	Larger studies with longer follow-up included in table 2.
Schaefer, A.; Seiffert, M.; Blankenberg, S. et al. (2020) Transapical mitral valve-in-ring procedure with a novel self-expandable transcatheter heart	Case report transapical mitral valve-in-ring procedure.	After implantation, fluoroscopy showed no residual	Larger studies included in table 2.

valve: First-and last-in-man report. European Journal of Cardio-thoracic Surgery; 58 (1); 190-192.		regurgitation and pressure measurements did not reveal any signs of left ventricular outflow tract obstruction.	
Sekaran N, Horne BD, Doty JR et al. (2021) Transcatheter mitral valve in ring, hazards of long anterior mitral leaflet and 3-dimensional rings. Catheterization and Cardiovascular Interventions; 97 (2); 353-358.	Retrospective case series N=22 transcatheter Mitral Valve in Ring (MViR) Follow up 1 year	Technical success was 57% (13/22), second transcatheter heart valves were needed in 7 patients. Procedure success at 30 days was achieved in 90.9% (20/22) patients. There were no procedural, in-hospital, or 30-day deaths. Two patients developed LVOT obstruction (1 had surgery and 1 had alcohol septal ablation). Anterior mitral leaflets (AMLs) were longer among 2 patients with LVOT obstruction (30mm). AML >25 mm increases the risk of MViR	Larger studies included in table 2.

		induced LVOT obstruction.	
Schaefer A, Conradi L (2020) Transcatheter Mitral Valve Replacement for Degenerated Bioprosthetic Valves and Failed Annuloplasty Rings. Surgical technology international; 37; 185-190.	Review of interventional techniques, evidence, and outcomes for transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annuloplasty rings.	Frequently used approaches for transcatheter mitral valve replacement include retrograde transapical and antegrade transseptal techniques, with Sapien valves, mechanical expandable Lotus valve, self-expandable transcatheter heart valves or dedicated transcatheter mitral valve replacement devices.	Review
Tanner RE, McCarthy J, Walsh KP et al. Transcatheter Mitral Valve-in-Ring Implantation. Irish Medical Journal. pg. 758	Case report 56-year woman with a failed mitral valve repair (annuloplasty ring) had a TMVIR delivered via the **trans-septal approach** using Sapien XT valve.	TOE at three months showed a well seated TAVI valve within the mitral annuloplasty ring with a trivial jet of paravalvular MR.	Larger studies with longer follow-up included in table 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.	Systematic review and meta-analysis	Pooled analyses of all VIV/VIR-TMVI studies demonstrated the 30-day	Outcomes for TMVIV and TMVIR not reported separately.

	17 eligible studies including a total of 1017 patients undergoing VIV/VIR-TMVI	mortality rate of 5.4% (95% CI, 4.0-6.8%), the midterm (1- to 5-year) mortality rate of 13.7% (95%CI, 9.0-18.5%), and significantly lower observed 30-day mortality than predicted operative mortality (RR, 0.67; 95% CI, 0.49-0.91; p= 0.01).	
Tiwana J, Aldea, G, Levin DB et al. (2020) Contemporary Transcatheter Mitral Valve Replacement for Mitral Annular Calcification or Ring. JACC: Cardiovascular Interventions; 13 (20); 2388-2398.	Case series (retrospective) Transcatheter mitral valve replacement (TMVR) for annular rings (n=12 TMVIR) and calcification (28 TViMAC) Follow up 30 days.	6 patients in TViMAC group died within 30 days and none in the ViRing group. 4 (14%) in the ViMAC group and 1 (8%) in the ViRing group had LVOT obstruction. 4 ViMAC and 1 ViRing had embolization or migration. Technical success was reported in 25 patients (63%): 9 in the ViRing and 16 in the ViMAC group. At 30 days, the mitral valve gradient was reduced. TViMAC and ViRing procedures	Larger studies included in table 2.

		frequently required use of adjunctive techniques (laceration of the anterior mitral valve leaflet, septal ablation).	
Toutouzas K, Lozos V, Oikonomou G (2018) Reduction of Para-Ring Regurgitation After Transcatheter Mitral Valve Replacement into a Failed Mitral Annuloplasty Ring. JACC: Cardiovascular Interventions, 11 (3), e17-e20	Case report 70-year old man with severe para-ring intravalvular mitral regurgitation due to partial dehiscence of the annuloplasty ring in the anterior mitral annulus and severe transvalvular mitral regurgitation due to malcoaptation of the valve leaflets had TMVIR procedure.	XT valve was successfully placed within the ring and was functioning well with mild paravalvular leak. Mean gradient of the prosthetic mitral valve was 6 mm Hg and there were no signs of LVOT obstruction. At 30-day follow-up, good function with no obstruction of the LVOT was noted.	Larger studies with longer follow-up included in table 2.
Wilbring M, Alexiou K, Tugtekin SM et al. (2015) Transapical transcatheter valve-in-ring implantation for failed mitral valve repair in the absence of radiopaque markers. J Thorac Cardiovasc Surg. 149(6): e92-4.	Case report 83-year old patient with failed mitral repair (annuloplasty ring) and severe mitral regurgitation underwent **transapical valve-in-ring** TMVIR.	At 1-year, excellent prosthesis function and only trace paravalvular regurgitation was reported. The patient remained in good clinical condition and showed no evidence	Larger studies with longer follow-up included in table 2.

		of cardiac-related morbidity.	
Wilbring M, Alexiou K, Tugtekin SM et al. (2014) Pushing the limits—further evolutions of transcatheter valve procedures in the mitral position, including valve-in-valve, valve-in-ring, and valve-in-native-ring. The Journal of Thoracic and Cardiovascular Surgery. 147 (1), 210-2019.	Case series N=14 patients had THV implantation in the mitral position (Sapien valves). (10 mitral valve-in-valve, **2 valve-in-ring procedures via transapical access**, 1 VIR via antegrade left-atrial access via right anterolateral minithoracotomy,1 surgical mitral valve replacement-valve in native ring).	Postoperative echocardiography on day 10 and after 6 weeks revealed good prosthesis function in all cases. Valve thrombosis occurred after 8 weeks and 3 months in 2 VIV patients. Results demonstrate feasibility of VIV and VIR procedures in the mitral position.	Larger studies included in table 2.
Wunderlich NC, Kische S, Ince H et al. (2014) Transcatheter Valve-in-Ring Implantation After a Failed Surgical Mitral Repair Using a Transseptal Approach and a Veno-Arterial Loop for Valve Placement. Catheterization and Cardiovascular Interventions 84:1202–1208.	case report TMVIR Implantation after a failed surgical mitral annuloplasty ring using a **transeptal approach** and a veno-arterial loop for placement.	Valve was positioned properly, and functional status improved.	Larger studies included in table 2.
Yoon SH, Whisenant BK, Bleiziffer S, et al. (2017) Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed	Case series (TMVR registry) N=248 TMVR in patients with failed mitral	Technical and device success rates were 92.3% and 85.5%. Compared with	Study included in systematic review added to table 2. A more recent

annuloplasty rings. J Am Coll Cardiol. 70:1121–1131	bioprosthetic valves (valve-in-valve [ViV=176]) and annuloplasty rings (valve-in-ring [ViR=72]).	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% 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 post procedural mitral regurgitation (19.4% vs. 6.8%; p = 0.003). 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	study from the same author is also included in table 2.

		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%; p = 0.01). Failed annuloplasty ring was independently associated with all-cause mortality (HR: 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	Study to identify the predictors of LVOT obstruction. Outcomes reported in another study added to table 2.

		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%.	