NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of valve-in-valve TAVI for aortic bioprosthetic valve dysfunction

The aortic valve controls the flow of blood out of the left chamber of the heart (left ventricle) to the body's main artery (aorta). A faulty aortic valve can be replaced with an artificial valve through open-heart surgery or by transcatheter aortic valve implantation (TAVI). If a bioprosthetic artificial valve (made of biological tissue) fails, another bioprosthetic valve can be placed inside it using a tube (catheter) inserted through a small cut in the skin and then through a large artery. This is known as valve-in-valve TAVI. The aim is to replace the faulty valve without the need for open-heart surgery.

Contents

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 specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2019.

Procedure name

- Valve-in-valve TAVI for aortic bioprosthetic valve dysfunction

Specialist societies

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

Description of the procedure

Indications and current treatment

The 2 main indications for aortic valve replacement are aortic stenosis and aortic regurgitation. Symptoms of both conditions typically include shortness of breath and chest pain on exertion. The increased cardiac workload can lead to heart failure.

Aortic valve replacement with an artificial prosthesis (biological or mechanical) is the conventional treatment for patients with severe aortic valve dysfunction. Valves may be placed by either open-heart surgery or using TAVI. Although bioprosthetic valves have some advantages over mechanical valves, they may degenerate and fail over time. The standard treatment for a failed bioprosthetic valve is open-heart surgery, with a further valve replacement. Reoperative surgery is associated with significant morbidity and a higher risk of mortality than primary surgery. Valve-in-valve (ViV)-TAVI has been developed as a less-invasive alternative treatment that avoids the need for cardiopulmonary bypass. It can be used for treating failed bioprosthetic aortic valves originally placed either by open-heart surgery or TAVI.

What the procedure involves

The procedure is done with the patient under general or local anaesthesia, with sedation using fluoroscopy. Prophylactic antibiotics and anticoagulant medication are used.

A new prosthetic valve is mounted within a stent, which is either self-expanding or expanded using balloon inflation. It is delivered by a catheter across the failed bioprosthetic aortic valve. Access to the aortic valve can be achieved transluminally, with entry to the circulation through the femoral or other large artery (sometimes known as a percutaneous, or endovascular approach), or through apical puncture of the left ventricle (a transapical or transventricular approach). In the transluminal approach, surgical exposure and closure of the artery may be needed. How access to the aortic valve is achieved depends on whether there are factors that make the passage of a catheter through the circulation difficult, such as peripheral arterial disease.

The procedure is technically similar to TAVI for aortic stenosis into a native aortic valve, but some modifications to the technique have been reported. The new prosthetic valve is placed tightly into the orifice of the failed bioprosthetic valve, pushing the old valve leaflets aside. Gradual valve deployment (without rapid inflation of the balloon) is done and angiography is used to ensure accurate positioning of the valve. The old prosthesis is also used as a guide for positioning the new valve. The external diameter of the new valve should usually match or exceed the internal diameter of the old valve.

Clinical assessment tools

Clinical assessment of severity of aortic stenosis

- New York Heart Association (NYHA) heart failure classification: this is used to classify the severity of breathlessness from class I, in which the patient has no limitation in daily physical activity, to class IV, in which the patient is breathless at rest.
- Haemodynamic assessment (usually by echocardiography and Doppler):
  - Aortic valve area (cm^2) or aortic valve area index (relative to body surface area; cm^2/m^2). An aortic valve area less than 0.6 cm^2/m^2 indicates severe aortic stenosis.
  - Transaortic gradient (mmHg). Peak transaortic valve gradient more than 64 mmHg and mean transaortic valve gradient more than 40 mmHg indicates severe aortic stenosis.
- The updated logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) II cardiac risk model is used for predicting mortality at the time

of cardiac surgery. It is based on logistic regression and takes account of multiple risk factor interactions.

Clinical assessment of severity of aortic regurgitation

Quantification by cardiac catheterisation

- Mild (grade 1+): a small amount of contrast enters the left ventricle during diastole and clears with each systole.
- Moderate (grade 2+): more contrast enters with each diastole and faint opacification of the entire left ventricular chamber occurs.
- Moderately severe (grade 3+): left ventricular chamber is well opacified and equal in density when compared with the ascending aorta.
- Severe (grade 4+): complete, dense opacification of the ventricular chamber on the first beat, and the left ventricle is more densely opacified than the ascending aorta.

Quantification by colour-flow Doppler

Jet height/left ventricular outflow tract (LVOT) height:

- Mild (1+): less than 25%
- Moderate (2+): 25–46%
- Moderately severe (3+): 47–64%
- Severe (4+): 65% or more

Regurgitant jet area/LVOT area:

- Mild (1+): less than 4%
- Moderate (2+): 4–24%
- Moderately severe (3+): 25–59%
- Severe (4+): 60% or more

Efficacy summary

ViV-TAVI in degenerated aortic surgical bioprosthesis

Technical success

In a systematic review and meta-analysis of 15 studies (861 patients, all study designs included, wide variety of devices used) of ViV-TAVI for surgical aortic bioprosthetic dysfunction, the pooled technical success rate was 95% (95% confidence interval [CI] 94% to 97%).[3]

In a case series (CoreValve U.S. Expanded Use Study) of 227 patients with failed surgical bioprostheses who had ViV-TAVI, technical success was achieved in 99% (225/227) patients. Device success was achieved in 93% (210/225) patients. Of the 15 patients who had device failure, 11 had more than 1 bioprosthesis implanted, 3 had isolated vascular access complications and 1 additional patient had multiple complications. Procedure success was achieved in 90% (203/225) patients. Of the 22 patients with procedural failure, 15 were because of device failure and 7 had in-hospital major adverse cardiovascular and cerebrovascular events.[7]

Survival

In a register of 459 patients who had ViV-TAVI for degenerated bioprosthetic valves, the 1-year survival rate calculated using a Kaplan−Meier curve was 83% (228/459; 95% CI 81% to 85%). Patients with stenosis of the valve had worse 1-year survival (77%; 95% CI 69% to 83%; 34 deaths, 86 survivors) compared with those with regurgitation (91%; 95% CI 86% to 97%; 10 deaths, 76 survivors) and those with mixed valve dysfunction (stenosis and regurgitation; 84%; 95% CI 77% to 91%, 18 deaths 66 survivors). Similarly, patients with small valves had worse 1-year survival after ViV-TAVI (75%; 95% CI 66% to 83%; 27 deaths; 57 survivors) than those with intermediate sized valves (82%; 95% CI 75% to 88%; 26 deaths; 92 survivors) or with large valves (93%; 95% CI 86% to 97%; 7 deaths; 73 survivors; p=0.001). Factors associated with mortality within 1 year included small size of the original surgical bioprosthesis (21 mm or less; hazard ratio [HR] 2.04; 95% CI 1.14 to 3.67; p=0.02) and aortic stenosis before intervention (compared with regurgitation, HR 3.07; 95% CI 1.33 to 7.08; p=0.008).[5]

Symptomatic improvement and quality of life

In the register of 459 patients, there was improvement in NYHA functional class after the procedure. Before treatment, 8% (35/459) of patients were in class I/II, compared with 93% (313/338) at 30-day follow up. Before treatment, 92% (424/459) of patients were class III/IV, compared with 7% (25/338) at 30 days. These results were maintained at 1-year follow up.[5]

In a PARTNER 2 valve-in-valve (ViV) registry of 365 patients with degenerated surgical aortic bioprostheses at high risk for reoperative surgery, patient symptoms improved from baseline to 30 days and 1 year. At baseline, more than 70% of patients were in NYHA functional class III or IV and at 30 days to 1 year more than 50% of the patients were in class I and 33% were in class II. In the same study, statistically significant improvements were seen in the summary Kansas City Cardiomyopathy Questionnaire (KCCQ) scores and 6-minute walk test distances. The mean overall summary KCCQ score increased from 43.0 (least squares: 40.7 to 45.3) at baseline, to 70.6 (68.2 to 72.9) at 30 days and 76.2 (73.5 to 78.8) at 1 year (p<0.0001); and mean 6-min walk test distance increased from 163.7 m (least squares: 145.8 to 181.7) at baseline to 229.3 m (211.2 to 247.5 m) at 30 days and 248.0 m (226.9 to 269.1 m) at 1 year (all p<0.0001). No differences in KCCQ scores were seen when patients were stratified according to bioprosthesis size or residual gradient.[6]

In the case series of 227 patients, there was a statistically significant improvement in quality of life as assessed by the KCCQ overall summary score. KCCQ scores increased from baseline to 30 days (D Δ 28.7) and persisted at 6 months (D Δ 30.8; p<0.001) and 1 year (D Δ 39.9; p<0.001). At 1-year follow up, 93% of patients were in NYHA functional class I or II.[7]

Haemodynamic improvement

In a systematic review and meta-analysis of 6 observational studies (4 unadjusted and 2 propensity matched studies; a total of 698 patients) comparing ViV-TAVI with redo-surgical aortic valve replacement (SAVR), the mean postoperative gradients were not statistically significantly elevated in the ViV-TAVI group compared with the redo-SAVR group (mean difference [MD] 0.81, 95% CI -4.53 to 6.15, p=0.77, I^2=91%).[1]

In a systematic review of 18 prospective and retrospective studies (823 patients) on ViV-TAVI, pooled analysis reported statistically significant improvements in mean gradient (from 36.9 mmHg preoperatively to 15.2 mmHg postoperatively, p<0.001) and peak gradient (from 59.2 preoperatively to 23.2 postoperatively, p=0.0003)[2]. Similar improvements were reported between ViV-TAVI and redo-SAVR groups (15.2 mmHg versus 13.5 mmHg, p=0.545). Statistically significant increases in postoperative pooled indexed effective orifice area (IEOA; p=0.004) and aortic valve area (p<0.0001) were also reported.[2]

In the PARTNER 2 ViV registry of 365 patients, mean effective orifice area (EOA) increased from baseline 0.93 cm^2 (95% CI 0.89 to 0.98) to 1.16 cm^2 (95% CI 1.11 to 1.21, p<0.0001) at 1-year follow up. Indexed EOA increased from baseline (0.49 cm^2/m^2, 95% CI 0.47 to 0.51 to 0.60 cm^2/m^2, 95% CI 0.57 to 0.63; p<0.0001) and mean gradient decreased from baseline (35.0 mmHg. 95% CI 33.7 to 36.2 to 17.6 mmHg. 95% CI 16.2 to 19.1, p<0.0001). When 30-day and 1-year data were compared, no statistically significant differences in mean EOA (1.13 cm^2 versus 1.16 cm^2, p=0.30) or mean gradient (17.7 mmHg versus 17.6 mmHg; p=0.90) were seen. Patients with stenotic bioprosthetic failure had higher 1-year mean gradient (18.9 mmHg versus 16.0 mmHg; p<0.0001) and lower indexed EOA (0.57 versus. 0.65 cm^2/m^2; p<0.0001) than those with regurgitant or mixed failure.[6]

In the case series of 227 patients, the mean aortic valve gradients reduced from 37.7 ± 18.1 mmHg at baseline to 17.0±8.8 mmHg at 30 days and 16.6±8.9 mmHg at 1 year. The EOA improved from 1.02 cm^2 at baseline to 1.41 cm^2 at 1-year follow up. Factors statistically significantly associated with higher discharge mean aortic gradients were surgical valve size, stenosis as modality of surgical bioprostheses failure and presence of surgical valve prosthesis-patient mismatch (all p<0.001).[7]

Aortic regurgitation

In the register of 459 patients, 5% (25/459) of patients had aortic regurgitation of at least moderate degree at 30-day follow up.[5]

In the PARTNER 2 ViV registry of 365 patients, at 1-year follow up, 5% patients had mild regurgitation and 3% had moderate regurgitation.[6]

In the case series of 227 patients, moderate aortic regurgitation occurred in 4% of patients at 30 days and 7% of patients at 1 year, with no severe aortic regurgitation.[7]

ViV-TAVI for rescue of suboptimal TAVI

Technical success

In a register of 663 patients, including 24 patients who had ViV-TAVI for aortic bioprosthesis malposition, procedural success was reported in all patients who had ViV-TAVI. This was defined as device deployment with fall of transaortic peak-to-peak gradient, without any periprocedural major adverse cardiovascular and cerebrovascular events (MACCE) within 24 hours of bioprosthesis implantation.[9]

Survival beyond 30 days

The register of 663 patients including 24 patients who had ViV for aortic bioprosthesis malposition reported that 1-year survival was 96% (23/24) in the ViV group.[9]

Symptomatic improvement

In the register of 663 patients including 24 patients who had ViV-TAVI for aortic bioprosthesis malposition, NHYA functional class III or IV at 1-year follow up was reported in 4% of patients in the ViV group.[9]

Haemodynamic improvement

In the register of 663 patients, including 24 patients who had ViV for aortic bioprosthesis malposition, at 1-year follow up, there was an improvement in the mean transaortic gradient in all 24 patients in the ViV group (from 45.4±14.8 mmHg to 10.5±5.2 mmHg, p=0.83).[9]

In a case series of 2,554 patients (including those who had TAVI in the PARTNER randomised controlled trial), 63 needed acute insertion of a second valve (ViV) as a rescue option, most commonly for post-procedural aortic regurgitation. Similar valve function was reported on follow-up echocardiography for those with ViV and without ViV.[10]

Aortic regurgitation

The register of 663 patients including 24 patients who had ViV reported that 8% (2/24) in VIV group had central aortic regurgitation at baseline (p=0.36). In all patients, no statistically significant central aortic regurgitation was reported at 1-year follow up.[9]

Safety summary

Mortality within 30 days

In the systematic review and meta-analysis of 6 observational studies , there was no statistically significant difference in perioperative mortality between the groups (5 [9/204] versus 6% [11/192], risk ratio [RR] 0.78, 95% CI 0.33 to 1.84, p=0.57, I^2=0%).[1]

In the systematic review of 18 studies (823 patients), the pooled incidence of perioperative 30-day all-cause mortality was similar for ViV-TAVI and redo-SAVR groups (6%, 95% CI 4.5 to 8.2% versus 6.5%, 95% CI 5.3 to 7.7, p=0.353).[2]

In a register of patients with high-risk aortic stenosis who had ViV-TAVI (n=1,150) matched to patients who had native valve (NV) TAVI (n=2,259), there were similar in-hospital mortality rates between the 2 groups (2% [24/1,150] versus 3% [62/,2,259], p=0.25). Mortality rates were higher in patients with small surgical valves, but there was no statistically significant difference in mortality based on the valve size used. In an unadjusted analysis, lower 30-day mortality was reported in the ViV-TAVI group compared with NV-TAVI group (HR 0.59, 95% CI 0.41 to 0.86, p=0.007). After adjustment, the 30-day mortality remained lower in the ViV group (HR 0.50, 95% CI 0.30 to 0.84, p<0.01).[4]

In the systematic review and meta-analysis of 15 studies (861 patients), the pooled 30-day mortality rate was 7% (95% CI 4% to 10%).[3]

In the transcatheter valve therapy (TVT) register of 459 patients, all-cause mortality rate was 8% (35/459) at 30-day follow up. Reasons for the deaths were not described.[5]

In the PARTNER 2 ViV registry of 365 patients, the rate of 30-day all-cause mortality was 3% (10/365). The rate of cardiovascular death was 3% (9/365). Mortality rates were less in additional patients enrolled in the continued access registry (n=269) compared with those included initially in the registry (n=92; 10% versus 20%, p=0.006).[6]

In the case series of 227 patients, the all-cause mortality rate was 2% (5/227) at 30-day follow up with no valve-related deaths. There were 4 procedural deaths (including 1 perforation, 1 tamponade from aortic dissection, 1 vascular complication, 1 coronary artery occlusion) and 1 non-cardiovascular death.[7]

Late mortality (median 1-year follow up)

In the systematic review and meta-analysis of 6 observational studies, there was no statistically significant difference in the rate of late mortality between the 2 groups (incident rate ratio [IRR] 0.93, 95% CI 0.74 to 1.16, p=0.51, I^2=0%).[1]

In the systematic review of 18 studies (823 patients), at latest follow up, overall ViV-TAVI all-cause mortality was 13% (95% CI 5.6 to 21.4, I^2=77.5%).[2]

In the register of patients with high-risk aortic stenosis who had ViV-TAVI (n=1,150) matched to patients who had a native valve (NV) TAVI (n=2,259), 1-year mortality was lower in the ViV-TAVI group compared with the NV-TAVI group in an adjusted analysis (HR 0.65, 95% CI 0.51 to 0.84, p<0.01). It was lower in younger (under 80 years) and older patients (over 80 years).[4]

In the systematic review and meta-analysis of 15 studies (861 patients), the 1-year mortality was 17% (95% CI 12% to 22%).[3]

In the PARTNER 2 ViV registry of 365 patients, the rate of 1-year all-cause mortality was 12% (43/365). Mortality rates were less in additional patients enrolled in the continued access registry (n=269) compared with those included initially in the registry (n=92; 20% versus 10%, p=0.0006).[6]

In the case series of 227 patients, the all-cause mortality rate was 15% (26/186) at 1 year, 1 of these was a valve-related death.[7]

In a case series of 226 patients with statistically significant paravalvular leakage (PVL) after TAVI with self-expanding valves, 1-year mortality was not statistically significantly different (22% versus 18% versus 25%; p=0.69) between patients without corrective measures (n=125) compared with patients who had had corrective measures (balloon post-dilation [n=85] or ViV-TAVI as a bailout procedure for a sub-optimally placed valve [n=16]).[8]

Ostial coronary obstruction

In the register of patients with high-risk aortic stenosis who had ViV-TAVI (n=1,150) matched to patients who had NV-TAVI (n=2,259), there was no difference in in-hospital coronary obstruction rates in the ViV-TAVI group compared with the NV-TAVI group (0.6% [7/1,150] versus 0.4% [9/2,259], p=0.37).[4]

In the register of 459 patients, ostial coronary obstruction was reported in less than 1% (2/459) of patients and was more frequent in the group of patients with aortic valve stenosis (4%; p=0.02; further details were not reported).[5]

In the PARTNER 2 ViV registry of 365 patients, the rate of 30-day coronary occlusion was 1% (3/365).[6]

In the case series of 227 patients, 1 patient experienced a coronary artery occlusion within 30 days.[7]

Stroke

In the systematic review and meta-analysis of 6 observational studies, there was no statistically significant difference in the rate of perioperative stroke between the groups (2% [3/204] versus 3% [5/192], RR 0.73, 95% CI 0.18 to 3.02, p=0.66, I^2=1%).[1]

In the systematic review of 18 studies (823 patients), the overall incidence of perioperative strokes was statistically significantly lower in ViV-TAVI compared with redo SAVR (2%, 95% CI 1.0 to 3.0. versus 5%, 95% CI 3.2 to 6.2, p=0.002). Overall cardiovascular related 30-day mortality in the ViV group was 5% (95% CI 3.4 to 6.5, I^2=0%).[2]

In the register of patients with high-risk aortic stenosis who had ViV-TAVI (n=1,150) matched to patients who had NV-TAVI (n=2,259), there was lower in-hospital stroke rate in the ViV-TAVI group (1% [14/1,150] versus 2% [54/2,259], p=0.02). In an unadjusted analysis, 30-day stroke rate in the ViV-TAVI group was also lower compared with NV-TAVI group (HR 0.58, 95% CI 0.36 to 0.93, p=0.025). After adjustment, the 30-day stroke rate remained lower in the ViV group (HR 0.56, 95% CI 0.30 to 1.04, p=0.06) but, at 1 year, there was no statistically significant difference (HR 0.78, 95% CI 0.47 to 1.29, p=0.34).[4]

In the systematic review and meta-analysis of 15 studies (861 patients), the pooled major stroke incidence was 2% (95% CI 1% to 3%).[3]

Major stroke within 30 days was reported in 2% (8/459) of patients in the register of 459 patients.[5]

In the PARTNER 2 ViV registry of 365 patients, the rate of all stroke at 30 days was 3% (10/365) and disabling stroke was 2%.[6]

In the case series of 227 patients, major stroke rate was less than 1% (1/227) at 30 days and 2% (3/186) at 1 year.[7]

In the case series of 226 patients with statistically significant PVL after TAVI with self-expanding valves, procedural stroke rate was not statistically significantly different (2% versus 2% versus 0%; p=0.82) between patients without corrective measures (n=125) compared with patients who had had corrective measures (balloon post-dilation [n=85] or ViV-TAVI as a bailout procedure for a sub-optimally placed valve [n=16]).[8]

Myocardial infarction

In the systematic review and meta-analysis of 6 observational, studies comparing ViV-TAVI with redo SAVR reported that there was no statistically significant difference in the rate of myocardial infarction between the groups (2% [4/182] versus 0.6% [1/170], RR 2.13, 95% CI 0.47 to 9.64, p=not significant).[1]

In the register of patients with high-risk aortic stenosis, who had ViV-TAVI (n=1,150) matched to patients who had V-TAVI (n=2,259), there was no statistically significant difference in the rate of in-hospital myocardial infarction between the groups (less than 1% [5/1,150] versus less than 1% [9/2,259], p=0.88).[4]

In the systematic review of 18 studies (823 patients), overall incidence of myocardial infarction in the ViV-TAVI group was 3% (95% CI 1.0 to 5.0, p=0.997, I^2=0%).[2]

In the PARTNER 2 ViV registry of 365 patients, the rate of myocardial infarction at 1-year follow up was 1% (5/365).[6]

In the case series of 227 patients, the rate of myocardial infarction at 30-day and 1-year follow up was 1% (2/227) and less than 1% (1/186).[7]

MACCE (this includes all-cause death, myocardial infarction, all stroke and reintervention)

In the case series of 227 patients with failed surgical bioprostheses who had ViV-TAVI, the MACCE rate was 4% (10/227) at 30 days and 19% (33/186) at 1-year follow up.[7]

Major adverse cerebrovascular and cardiac event rates of 0% and 5% were reported at 30-day and 1-year follow up respectively in 24 patients who had ViV-TAVI in a register of 663 patients.[9]

Heart failure

In the register of patients with high-risk aortic stenosis who had ViV-TAVI (n=1,150) matched to patients who had NV-TAVI (n=2,259), there were fewer hospitalisations for heart failure at 30 days in the ViV-TAVI group compared with the NV-TAVI group in an unadjusted analysis (HR 0.52, 95% CI 0.35 to 0.77, p=0.77). After adjustment, the rates at 30 days remained lower in the ViV group

(HR 0.60, 95% CI 0.35 to 1.02, p=0.06) and it was statistically significantly lower at 1 year (HR 0.68; 95% CI 0.50 to 0.94, p=0.02).[4]

Implantation of a second ViV prosthesis

In the register of patients with high-risk aortic stenosis who had ViV-TAVI (n=1,150) matched to patients who had NV-TAVI (n=2,259), the in-hospital aortic valve reintervention rates were lower (less than 1% [3/1,150] versus less than 1% [13/2,259], p=0.20) and, in an unadjusted analysis, at 30 days in the ViV-TAVI and NV-TAVI groups (HR 0.65, 95% CI 0.27 to 1.56, p=0.339). After adjustment, the rates at 30 days (HR 0.33, 95% CI 0.09 to 1.15, p=0.08) and 1 year (HR 0.52; 95% CI 0.20 to 0.1.33, p=0.17) were not statistically different between the 2 groups.[4]

Implantation of a second transcatheter valve was needed in 6% (26/459) of patients and retrieval of a self-expanding valve was needed in 10% (21/213) of procedures in the register of 459 patients.[5]

In the case series of 227 patients, 4% (10/227) patients needed implantation of more than 1 valve.[7]

Need for a permanent pacemaker

In the systematic review and meta-analysis of 6 observational studies, the rate of permanent pacemaker insertion was statistically significantly lower in the ViV-TAVI group compared with redo-SAVR group (8% [17/204] versus 15% [28/192], RR 0.57, 95% CI 0.32 to 1.0, p=0.05, I^2=0%).[1]

In the systematic review of 18 studies (823 patients), the pooled incidence of permanent pacemaker implantations was similar between the ViV group and redo-SAVR group (7% [95% CI 4.3 to 8.7] versus 8% [95% CI 2.9 to 13.5], p=0.257).[2]

In the register of patients with high-risk aortic stenosis, who had ViV-TAVI (n=1,150) matched to patients who NV-TAVI (n=2,259). in-hospital permanent pacemaker rates were lower in the ViV-TAVI group compared with the NV-TAVI group (3% [34/1,150] versus 11% [246/2,259], p<0.001).[4]

In the systematic review and meta-analysis of 15 studies (861 patients), the pooled permanent pacemaker rate was 8% (95% CI 6% to 10%).[3]

Permanent pacemaker implantation was needed in 8% (38/459) of patients in the register of 459 patients.[5]

In the PARTNER 2 ViV registry of 365 patients, the rate of new pacemaker implantation at 30 days was 2% (7/365) and at 1 year 3% (9/365).[6]

In the case series of 227 patients, the rate of new permanent pacemaker implantation was 8% (18/227) at 30 days and 11% (19/186) at 1 year.[7]

Acute kidney injury

In the systematic review and meta-analysis of 6 observational studies, there was no statistically significant difference in the rate of acute kidney injury between the groups (8% [14/176] versus 12% [20/166], RR 0.71, 95% CI 0.22 to 2.33)[1].

In the systematic review of 18 studies (823 patients), the pooled incidence of acute kidney injury was similar between the ViV-TAVI group and redo-SAVR group (7%, 95% CI 5.1 to 8.9, versus 9%, 95% CI 4.4 to 12.8, p=0.927).[2]

In the systematic review and meta-analysis of 15 studies (861 patients), the pooled renal failure incidence was 7% (95% CI 5% to 9%).[3]

Acute kidney injury was reported in 7% (34/459) of patients in the register of 459 patients (further details were not reported).[5]

In the PARTNER 2 ViV registry of 365 patients, the rate of acute kidney injury at 30 days was 8% (27/365) and at 1 year 9% (31/365).[6]

In the case series of 227 patients, the rate of acute kidney injury was 4% (9/227) at 30 days and 4% (7/186) at 1 year.[7]

Paravalvular regurgitation

In the systematic review and meta-analysis of 6 observational, mild or greater paravalvular regurgitation was statistically significantly higher in the ViV-TAVI group compared with the redo-SAVR group (21% [36/171] versus 6% [8/145], RR 3.83, 95% CI 1.2 to 12.22, p=0.02)[1].

In the systematic review of 18 studies (823 patients), the pooled incidence of moderate PVL were statistically significantly higher for ViV-TAVI compared with redo SAVR (3% [95% CI 0.9 to 5.8] versus less than 1%, 95% CI 0 to 1.], p=0.022). The rates for mild PVL were not statistically significantly different (10%, 95% CI 3.1 to 16.3, versus less than 1%, 95% CI 0 to 1.1, p=0.175).[2]

In the PARTNER 2 ViV registry of 365 patients, at 1-year follow up, the rate of moderate paravalvular aortic regurgitation was 1% (1/105) and the rate of mild paravalvular aortic regurgitation was 5% (5/105).[6]

Paraprosthetic leak (grade 2+ or more) was reported in 4% (1/24) of patients in the ViV group in the register of 663 patients.[9]

Severe patient–prosthesis mismatch

In the systematic review and meta-analysis of 6 observational studies, the incidence of severe patient–prosthesis mismatch was statistically significantly higher in the ViV-TAVI group compared with the redo-SAVR group (21% [14/104] versus 3% [3/92], RR 3.67, 95% CI 1.17 to 11.54, p=0.03, I^2=0%)[1].

Severe patient–prosthesis mismatch (clinical consequences not described) occurred in 32% of patients surviving ViV procedure in the register of 459 patients. The incidence was lower in patients with bioprosthetic regurgitation at baseline than in those with stenosis and combined valve dysfunction (19% compared with 36% and 36%; p=0.03).[5]

In the PARTNER 2 ViV registry of 365 patients, severe patient–prosthesis mismatch (defined as IEOA less than 0.65 cm^2/m^2) was reported in 58% patients.[6]

Major bleeding

In the systematic review and meta-analysis of 6 observational studies, there was no statistically significant difference in the rate of major bleeding between the groups (12% [12/104] versus 27% [25/92], RR 0.48, 95% CI 0.16 to 1.50)[1].

In the systematic review of 18 studies (823 patients), overall bleeding rates were statistically significantly lower in ViV-TAVI compared with redo SAVR (5%, 95% CI 1.7 to 7.4, versus 9%, 95% CI 6.7 to 11.3, p=0.014).[2]

In the register of patients with high-risk aortic stenosis who had ViV-TAVI (n=1,150) matched to patients who had NV-TAVI (n=2,259), in-hospital major bleeding rates were lower in the ViV-TAVI group compared with the NV-TAVI group (3% [38/1,150] versus 5% [117/2,259], p=0.013).[4]

In the systematic review and meta-analysis of 15 studies (861 patients), the pooled major bleeding incidence was 6% (95% CI 4% to 7%).[3]

Major bleeding was reported in 8% (37/459) of patients in the register of 459 patients (further details were not reported).[5]

In the PARTNER 2 ViV registry of 365 patients, the rate of major bleeding at 30 days was 1% (76/365) and at 1 year 23% (84/365).[6]

In the case series of 227 patients with failed surgical bioprostheses who had ViV-TAVI the rate of major bleeding was 15% (33/227) at 30 days and 16% (29/186) at 1 year.[7]

Major vascular complications

In the systematic review and meta-analysis of 6 observational studies, there was no statistically significant difference in the rate of major vascular complications between the groups (7% [10/154] versus 2% [3/144], RR 2.53, 95% CI 0.79 to 8.16)[1].

In the register of patients with high-risk aortic stenosis who had ViV-TAVI (n=1,150) matched to patients who had NV-TAVI (n=2,259), in-hospital vascular complication rates were lower in the ViV-TAVI group compared with the NV-TAVI group (3% [35/1,150] versus 5% [109/2,259], p=0.014).[4]

In the systematic review of 18 studies (823 patients), the pooled incidence of major vascular complications in the ViV group was 5% (95% CI 3% to 8%), p=0.936, I^2=0%).[2]

Major vascular complications were reported in 9% (42/459) of patients in the register of 459 patients (further details were not reported).[5]

In the PARTNER 2 ViV registry of 365 patients, the rate of major vascular complications at 30 days was 4% (15/365) and at 1 year 4% (16/365).[6]

In the case series of 227 patients, the rate of major vascular complications was 10% (23/227) at 30 days and 11% (21/186) at 1 year.[7]

New atrial fibrillation

In the systematic review and meta-analysis of 6 observational studies, the rate of new onset atrial fibrillation was statistically significantly lower in the ViV-TAVI group compared with the redo-SAVR group (16% [8/49] versus 45% [21/47], RR 0.37, 95% CI 0.18 to 0.76, p=0.007, I^2=0%).[1]

In the register of patients with high-risk aortic stenosis who had ViV-TAVI (n=1,150) matched to patients who had NV-TAVI (n=2,259), in-hospital atrial fibrillation rates were lower in the ViV-TAVI group compared with the NV-TAVI group (2% [22/1,150] versus 5% [113/2,259], p<0.001).[4]

New onset dialysis

In the systematic review and meta-analysis of 6 observational studies, the rate of new onset dialysis was statistically significantly lower in the ViV-TAVI group compared with redo-SAVR group (3% [5/155] versus 10% [15/145], RR 0.35, 95% CI 0.13 to 0.90, p=0.03, I^2=0%).[1]

Conversion to SAVR

In the register of patients with high-risk aortic stenosis, who had ViV-TAVI (n=1,150) matched to patients who had NV-TAVI (n=2,259), there was no statistically significant difference between the groups in the rate of conversion to open-heart surgery during the procedure (0.2% [2/1,150] versus 0.4% [9/2,259], p=0.28).[4]

In the PARTNER 2 ViV registry of 365 patients, the rate of conversion to surgery at 30 days was less than 1%.[6]

In the case series of 227 patients, the rate of surgical reintervention within 30 days was less than 1%[7]

Other events

In the register of patients with high-risk aortic stenosis, who had ViV-TAVI (n=1,150) matched to patients who had NV-TAVI (n=2,259), there was no statistically significant difference between the groups in the rates of device embolisation (p=0.34), perforation (0.20), aortic dissection (0.38), annular rupture (0.22) during the procedure.[4]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers 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, specialist advisers listed the following anecdotal adverse event: femoral and iliac vessel injury. They considered that the following was a theoretical adverse event: valve durability.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to valve-in-valve TAVI for aortic bioprosthetic valve dysfunction. The following databases were searched, covering the period from their start to 21.08.2018: 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 following selection criteria (table 1) 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.

Table 1 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 aortic bioprosthetic valve dysfunction.
Intervention/test	Valve-in-valve TAVI.
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 4,256 patients from 3 systematic reviews and meta-analysis[1-3] and 8 case series (registry data)[4-11].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on valve-in-valve TAVI for aortic bioprosthetic valve dysfunction

Studies of patients with degenerated aortic surgical bioprosthesis

Study 1 Tam DY (2018)

Details

Study type	**Systematic review and meta-analysis**
Country	Canada
Study period	Databases searched and period: Medline and Embase searched from 1946 to 2017. References of original articles reviewed manually.
Study population and number	n=**6 retrospective observational studies (498 patients)- 4 unadjusted[n=298] and 2 propensity matched [n=200] studies** (Grubitshch 2017, Silaschi 2017, Spaziano 2017, Ejiofor 2016, Santarpino 2016, Erlebach 2015) **comparing ViV-TAVI (n=254) versus redo SAVR (n=244) for previously failed aortic bioprostheses** Bioprosthesis mode of failure (according to ASE): not reported Type of degenerated bioprosthesis: not reported Surgical valve size; there were more patients with smaller valve sizes (<21mm) reported in the redo-SAVR group in 2 studies that reported failed valve size. Baseline risk scores: 23% higher in ViV group compared to redo SAVR (ratio of means 1.34; 95% CI 1.02 to 1.48; p=0.03). Comorbidities: ViV group had a statistically significantly higher incidence of coronary artery disease, coronary artery bypass grafting, and chronic renal disease. Time to valve deterioration from index procedure: not reported
Age and sex	Mean age in studies ranged from 66 to 80 years; ViV patients were older than redo-SAVR patients (mean difference 2.85 years, 95% CI 0.26-5.43, p=0.03). More than half of the ViV patients were male
Study selection criteria	Inclusion criteria: comparison of ViV to redo SAVR and at least one outcome of interest. Exclusion criteria: conference proceedings, or non-comparative study designs
Technique	ViV-TAVI access: a variety of access sites were used, but the most commonly used are the transfemoral (>50%) and transapical (39%) approaches. Other approaches used are subclavian (<1%), and transaortic (6%). Redo SAVR: median sternotomy was performed in all cases. Devices: varied widely, studies used a mix of TAVI valve systems, mainly first generation TAVI devices (CoreValve, Sapien, XT, Lotus, JenaValve, Engager, and Portico). Sapien and Sapein XT valves were frequently used. One study (Santarpino 2016) had sutureless (Perceval) degenerated valves.
Follow up	**Median 1 year (range 0.5 to 3 years)**
Conflict of interest/source of funding	No conflict of interest; one author received funding from Edwards Life Sciences and Medtronic and an award from Heart and Stroke Foundation of Canada. One author received funding from the Ontario Ministry of Health.

Analysis

Follow-up issues: short follow-up period, minimal loss to follow up was reported in 4 studies.

Study design issues: 2 reviewers screened and abstracted data from selected articles. Any disagreements were resolved by consensus. End points were defined using Valve Academic Research Consortium (VARC and VARC-2) definitions. Severe patient−prosthesis mismatch was defined as an indexed effective orifice area (IEOA)<0.65 cm^2/m^2. Risk of bias in studies was assessed using GRADE approach and were rated as moderate to high quality. Random effects meta-analysis was done.

All were retrospective observational studies and only 2 studies used propensity score matching. Data was collected from surgical databases or clinic charts and 5 studies had concurrent controls drawn from the study period. Treatment was according to clinical team decision. Only 1 study was from UK.

Study population issues: there was overlap in patients in the study by Spaziano 2017 and Erlebach 2015. Data from Spaziano was mainly used as the sample size was larger but outcomes not reported in the Spaziano were taken from Erlebach 2015.

Other issues: patients in ViV group were often of high risk for surgery and more likely to have a smaller failed bioprosthetic valve (<23mm).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr>
<td>
Number of patients analysed: 6 studies [ViV-TAVI (n=254) versus redo SAVR (n=244)]
Mean procedure time (2 studies)
The mean procedure time in ViV-TAVI group ranged from 100 to 100.6 minutes while the mean surgical procedure time ranged from 250 to 269 minutes.
ICU and hospital length of stay
There was a pooled reduction of 1.8 days in ICU length of stay (MD -1.79, 95% CI -2.41 to -1.16; p<0.00001; I^2=0%) and 5.0 days in total hospital length of stay (MD: -5.04, 95% CI -7.22 to -2.86; p<0.00001; I^2=15%) in the ViV-TAVI group compared to the redo-SAVR group.
Echocardiographic outcomes
The mean postoperative aortic valvular gradients (>20 mmHg) were not statistically significantly elevated in the ViV-TAVI group (MD; 0.81, 95% CI -4.53 to 6.15; p=0.77; I^2=91%) compared to redo SAVR group.
</td>
<td>
Perioperative outcomes
<table>
<tr><th>ViV event rate % (n)</th><th>Redo SAVR event rate % (n)</th><th>P value, I^2</th><th>RR (95% CI)</th></tr>
<tr><td colspan="4">30 day/in-hospital mortality</td></tr>
<tr><td>4.5 (9/204)</td><td>5.7 (11/192)</td><td>0.57, I^2=0%</td><td>0.78 (0.33, 1.84)</td></tr>
<tr><td colspan="4">Myocardial infarction</td></tr>
<tr><td>2.2 (4/182)</td><td>0.6 (1/170)</td><td>NS</td><td>2.13 (0.47, 9.64)</td></tr>
<tr><td colspan="4">Any stroke</td></tr>
<tr><td>1.5 (3/204)</td><td>2.6 (5/192)</td><td>0.66, I^2=1%</td><td>0.73 (0.18, 3.02)</td></tr>
<tr><td colspan="4">Disabling stroke</td></tr>
<tr><td>1.7 (3/176)</td><td>3.6 (6/166)</td><td></td><td>0.62 (0.16,2.42)</td></tr>
<tr><td colspan="4">Permanent pacemaker implantation</td></tr>
<tr><td>8.3 (17/204)</td><td>14.6 (28/192)</td><td>0.05, I^2=0%</td><td>0.57 (0.32,1)</td></tr>
<tr><td colspan="4">Atrial fibrillation</td></tr>
<tr><td>16.3 (8/49)</td><td>44.7 (21/47)</td><td>0.007, I^2=0%</td><td>0.37 (0.18, 0.76)</td></tr>
<tr><td colspan="4">Major vascular complications</td></tr>
<tr><td>6.5 (10/154)</td><td>2.1 (3/144)</td><td>NS</td><td>2.53 (0.79,8.16)</td></tr>
<tr><td colspan="4">Life-threatening or major bleeding</td></tr>
<tr><td>11.5 (12/104)</td><td>27.2 (25/92)</td><td>NS</td><td>0.48 (0.16,1.5)</td></tr>
<tr><td colspan="4">New onset Dialysis</td></tr>
<tr><td>3.2 (5/155)</td><td>10.3 (15/145)</td><td>0.003, I^2=0%</td><td>0.35 (0.13, 0.9)</td></tr>
<tr><td colspan="4">Acute kidney injury (AKIN 2 or 3)</td></tr>
<tr><td>8.0 (14/176)</td><td>12.0 (20/166)</td><td></td><td>0.71 (0.22, 2.33)</td></tr>
<tr><td colspan="4">Paravalvular leak (mild or greater)</td></tr>
</table>
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</tr>
</table>

21.1 (36/171)	5.5 (8/145)	0.02	3.83 (1.2, 12.22)
Severe patient−prosthesis mismatch (IEOA<0.65)			
21.1 (14/104)	3.3 (3/92)	0.03, I^2=0%	3.67 (1.17, 11.54)

Late (>30 days) mortality (all studies)

There was no statistically significant difference in late mortality between the groups, but heterogeneity was substantial (RR 0.93, 95% CI 0.74- 1.16, p=0.51, I^2=0%).

Abbreviations used: AKIN, Acute Kidney Injury Network Class; CI, confidence interval; ICU, intensive care unit; MD, mean difference; NS, not significant; RR, relative risk; redo-SAVR, redo-surgical aortic valve replacement; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.

Study 2 Phan K (2016)

Details

Study type	**Systematic review and meta-analysis**
Country	Australia and Italy
Study period	Databases searched and period: Medline, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane database of Systematic Reviews (CDSR), ACP journal and Database of Abstracts of Review of effectiveness (DARE) were searched from inception to 2015. References of selected articles were reviewed manually. Experts were consulted for unpublished data.
Study population and number	n=**18 studies (823 patients)** **8 prospective studies and 10 retrospective studies** **comparing ViV-TAVI versus redo SAVR for previously failed aortic bioprostheses** Bioprosthesis mode of failure (according to ASE): VIV group: aortic stenosis 39%, regurgitation 33.7%. Type of degenerated bioprosthesis: not reported Surgical valve size; VIV group: mean 24.6mm. Mean Logistic EuroSCORE %: ViV group 31; redo-SAVR group 26. Comorbidities: prevalence of hypertension, diabetes, chronic kidney disease and peripheral vascular disease was higher in the VIV group. 50% patients had coronary artery disease, and 15% had a history of stroke and 31% had previous CABG in both groups. Time to valve deterioration from index procedure: not reported
Age and sex	Age: VIV group: pooled mean 77.5 years (range 68-82 years); redo-SAVR group: mean age 66.7 years Sex: ViV group: 58% male; redo SAVR 57.6% male
Study selection criteria	Inclusion criteria: English studies in which patients had ViV-TAVI. Exclusion criteria: studies with less than 10 patients, abstracts, conference proceedings, reviews, case reports, expert opinions and duplicate studies were excluded.
Technique	ViV-TAVI Access: a variety of access sites were used, but the most commonly used are the transfemoral and transapical approaches. Other approaches used are subclavian and transaortic. Devices: varied widely, studies used a mix of TAVI valve systems, mainly first generation TAVI devices (CoreValve, Sapien, Sapein XT, Engager) valves were frequently used.
Follow up	**Mean 1 year in 8 studies (range 1 month to 33 months)**
Conflict of interest/source of funding	None to declare

Analysis

Follow-up issues: short term follow up in included studies.

Study design issues: PRISMA guidelines were followed to conduct this systematic review. Two reviewers screened and abstracted data from selected articles. Any disagreements were resolved by consensus. For comparison between ViV-TAVI and redo SAVR, data from a recent review on SAVR outcomes was used. As studies were small, a mixed effects meta-regression with a fixed effect moderate variable was done. The quality of studies was assessed using National Health Service Centre for reviews and dissemination case series quality assessment criteria. MOOSE checklist of the Dutch Cochrane review group was also used.

Study population issues: indications in patients across the studies were heterogeneous.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **18 studies [ViV-TAVI versus redo SAVR]**

Operative outcomes for ViV-TAVI implantation

Pooled procedural time (minutes)	87.8 (95% CI 70.7-104.9, I^2=92%)
Average fluoroscopy time (minutes)	16.8 (95% CI 6.9-30.8, I^2=99.5%)
Average hospital stay (days)	9.7 (95% CI 7.6-21.4, I^2=77.5%)

Haemodynamic outcomes

ViV event rate % (n)	**Pooled estimate (95% CI), P value, I^2**	**Redo SAVR event rate % (n)**	**Pooled estimate (95% CI), P value, I^2**	**P value**
Postoperative mean peak gradient (mmHg)				
-	15.2 (13.4-17.1, p<0.001, I^2=89%)	-	13.5 (6.8-20.3, p<0.001, I^2=99%)	0.545
Postoperative peak gradient (mmHg)				
	23.2	NA	NA	NA

In the ViV group, preoperative mean gradient was 36.9 mmHg and peak gradient was 59 mmHg. The postoperative values were statistically significantly lower compared to preoperative values (p<0.0001, p=0.0003). Statistically significant increases in the IEOA (p=0.004) and the AVA (p<0.0001) were noted.

Safety

Perioperative outcomes

ViV event rate % (n)	**Pooled estimate (95% CI), P value, I^2**	**Redo SAVR event rate % (n)**	**Pooled estimate (95% CI), P value, I^2**	**P value**
Perioperative 30-day all-cause mortality				
7.9 (65/823)	6.4 (4.5-8.2), p=0.39, I^2=4.8%	6.1 (38/626)	6.5 (5.3-7.7), p<0.001, I^2=51%	0.353
All-cause mortality at latest follow up				
	12.6 (5.6-21.4, I^2=77.5%)	NA	NA	NA
Cardiovascular related 30-day mortality				
	4.9 (3.4-6.5), I^2=0%	NA	NA	NA
Myocardial infarction				
2.2 (6/271)	3.0 (1.0-5.0), p=0.997, I^2=0%	NA	NA	NA
Any stroke				
1.9 (15/802)	2.0 (1.0-3.0), p=0.998, I^2=0%	8.8 (40/793)	4.7 (3.2-6.2), p=0.713, I^2=0%	0.002
Bleeding				
6.9 (47/681)	4.6 (1.7-7.4), p=0.029, I^2=51.6%	9.1 (53/585)	9.0 (6.7-11.3), p=0.911, I^2=0%	0.014
Permanent pacemaker implantation				
8.2 (66/802)	6.5 (4.3-8.7),p=0.258, I^2=17%	9.2 (61/662)	8.2 (2.9-13.5), p<0.001, I^2=86%	00.257
Vascular complications				
7.7 (49/634)	5.4 (2.6-8.1), p=0.156, I^2=32%	NA	NA	NA
Acute kidney injury (AKIN 2 or 3)				
7.5 (52/697)	7.0 (5.1-8.9), p=0.936, I^2=0%	8.4 (62/740)	8.6 (4.4-12.8), p=0.001, I^2=79%	0.927
Mild paravalvular leak				
13.1 (26/199)	9.7 (3.1-16.3), p<0.001, I^2=76%	0 (0/220)	0.4 (0-1.1), p=0.646, I^2=0%	0.175
Moderate paravalvular leak				

		3.5 (71/199)	3.3 (0.9-5.8), p=0.936, I^2=0%	0 (0/220)	0.4 (0-1.1), p=0.646, I^2=0%	0.022	

Abbreviations used: AKIN, Acute Kidney Injury Network Class; AVA, aortic valve area; CI, confidence interval; IEOA, indexed effective orifice area; NA, not available; redo SAVR, redo-surgical aortic valve replacement; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.

Study 3 Chen HL (2016)

Details

Study type	**Systematic review and meta-analysis**
Country	China
Study period	Databases searched and period: Medline, from inception to 2015.
Study population and number	n=**15 studies (861 patients) on ViV-TAVI for surgical aortic bioprosthetic dysfunction.** Bioprosthesis mode of failure (according to ASE): not reported Type of degenerated bioprosthesis: not reported Surgical valve size; not reported Mean Logistic EuroSCORE %: not reported Comorbidities: not reported Time to valve deterioration from index procedure: not reported
Age and sex	Age: range 69-82 years; Sex: more than 50% male
Study selection criteria	Inclusion criteria: studies that reported early and late clinical outcomes on ViV-TAVI in treating surgical bioprosthetic dysfunction. Exclusion criteria: reviews, editorials and letters were excluded.
Technique	ViV-TAVI access: a variety of access sites were used, but the most commonly used are the transfemoral and transapical approaches. Other approaches used are subclavian, transaxillary and transaortic. Devices: varied widely, studies used a mix of TAVI valve systems, mainly first generation TAVI (CoreValve, Sapien, Sapein XT, JenaValve) valves were frequently used.
Follow up	**Mean 1 year (range 1 month to 8 years)**
Conflict of interest/source of funding	None to declare, work was funded by the Nantong Municipal Science and Technology Bureau.

Analysis

Follow-up issues: Studies were small with less than 1-year follow up.

Study design issues: 2 reviewers screened and abstracted data from selected articles. Any disagreements were resolved by consensus. The quality of studies was not assessed. Meta-analysis was done using random and fixed effects methods. A subgroup analysis was done by dysfunction valve position (aortic or mitral). Substantial heterogeneity was found between studies in many outcomes.

Other issues: data on mitral valve dysfunction were not extracted as it is out of the scope of this assessment.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **15 studies ViV-TAVI** **Successful rate of ViV-TAVI in treating aortic prosthetic valve dysfunction** Subgroup analyses showed that the pooled successful rate was 95.4% (95% CI 93.9-96.7%).	**Early and late clinical outcomes (pooled rates)**

	% (95% CI)
30-day mortality	6.9 (4.3-10.0)
Major stroke incidence	1.8 (1.0-2.8)
Renal failure incidence	6.7 (5.1-8.6)
Major bleeding incidence	5.5 (4.0-7.2)
Permanent pacemaker incidence	7.6 (5.9-9.6)
1-year mortality	16.5 (12.0-21.6)

Abbreviations used: CI, confidence interval; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.

Study 4 Tuzcu EM (2018)

Details

Study type	**Case series (retrospective data)** **Transcatheter valve therapies (TVT) registry** (by STS and American College of Cardiology in collaboration with FDA, centres for Medicare and Medicaid Services and industry)
Country	USA
Recruitment period	2011 to 2016
Study population and number	n=**3,409 patients with high-risk aortic stenosis** **ViV-TAVI for failed SAVR (n=1,150) compared with native valve (NV) TAVI for aortic valve stenosis (n=2,259)** Bioprosthesis mode of failure (according to ASE): ViV-TAVI group: stenosis (61%, 702/1,150), regurgitation (12.2%, 140/1,150), or combined stenosis and regurgitation (24.6%, 283/1,150). Type of degenerated bioprosthesis: not reported Surgical valve size (ViV-TAVI group [n=868]):<21mm: 34.7% (301/1,150),>21 and<25 mm: 54.9% (477/1,150),>25 mm:10.1% (88/1,150) STS score: ViV-TAVI 6.9%; NV-TAVI 6.8% NYHA functional class III-IV: ViV-TAVI 85.4% (971/1,150); NV-TAVI 81% (1826/2,259), p=0.003 Mean time from last SAVR-VIV: not reported
Age and sex	Age: ViV-TAVI mean 79 years; NV-TAVI mean 84 years Sex: ViV-TAVI 60% (700/1,150) male; NV-TAVI 61% (1377/2,259) male
Patient selection criteria	Patients having ViV-TAVI from 2011-16 matched on sex, high or extreme risk, hostile chest or porcelain aorta, 5-minute walk test, and Society of Thoracic Surgeons [STS] predicted risk of mortality (PROM) for reoperation in a 1:2 fashion in patients having NV-TAVI.
Technique	Technique: ViV-TAVI Devices: balloon valves (n=501, 20mm, 23mm, 26mm, 29mm) (Sapein XT and S3, Evolut R and CoreValve) and self-expandable valves (n=647, 23mm, 26mm, 29mm, 31mm) used. Access: transfemoral: ViV-TAVI 88.2% (1014/1,150) versus NV-SAVR 80.1% (1809/2,259). Non-transfemoral approach was more in NV-SAVR group.
Follow up	**1 year**
Conflict of interest/source of funding	Authors report receiving grants, serving as speakers and consultants for different manufacturers. Some were investigators in research trails sponsored by manufacturers.

Analysis

Study issues: retrospective analysis of data from individual centres. Baseline and in-hospital data according to Valve Academic Research Consortium 1 and 2 definitions were obtained via case reports from the TVT registry. Death, stroke and other intervention events were decided by cardiologists at the analysis centre. The 30 day and 1-year outcomes were obtained from the linked Medicare administrative claims data.

Patient issues: patients in the ViV-TAVI group had more previous cardiac surgeries, bypass surgery, non-aortic valve surgery. The group also had more frequently moderate or severe mitral regurgitation, tricuspid regurgitation, permanent pacemaker and lower left ventricular ejection fraction. Patients in the NV-TAVI group had high rates of diabetes, coronary artery disease, percutaneous coronary intervention and peripheral vascular disease and needed a non-transfemoral approach.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **ViV-TAVI for failed SAVR (n=1,150) compared with native valve (NV) TAVI for aortic valve stenosis (n=2,259)**

Procedural outcomes

	ViV-TAVI group (n=1,150)	**NV-SAVR group (n=2,259)**	**p value**
General anaesthesia use %	78.7	83.7%	<0.001
Fluoroscopy time, minutes	21	18	<0.001
Contrast volume, ml	60	105	<0.001
Discharge to home % (n)	84.8 (955)	71.4 (1568)	<0.001
Length of stay, days	3.0 (2.0-5.0)	4.0 (3.0-6.0)	<0.001

Echocardiographic outcomes

	ViV-TAVI group (n=1,150)	**NV-SAVR group (n=2,259)**	**p value**
Mean aortic valve gradient (AVG) mmHg^	16 (10-22	9 (6-12)	<0.001
Mean aortic valve area, cm^2	1.3 (1.1-1.8)	1.8 (1.4-2.2)	<0.001
Aortic regurgitation			
None % (n)	55 (602)	37.4 (796)	NR
Trace % (n)	24.7 (271)	26 (552)	NR
Mild % (n)	16.8 (184)	30 (639)	NR
Moderate % (n)	3.0 (33)	5.8 (124)	NR
Severe % (n)	0.5 (5)	0.8 (16)	NR

^ The mean AVG decreased statistically significantly after the procedure (ViV-TAVI from 40 to 16mmHg, NV-SAVR from 42 to 9 mmHg, p<0.01). It was different in patients with different modes of failure in the ViV-TAVI group (17mmHg, 12mmHg, and 15mmHg in the stenosis, regurgitant and combined group). Mean AVG were higher in patients with smaller surgical prosthesis, and in those with smaller valves used. Gradients also differed by the type of valve used (balloon expandable or self-expanding).

Safety

In-hospital outcomes % (n)

	ViV-TAVI	**NV-TAVI**	**P value**
Death	2.1 (24)	2.7 (62)	0.25
Any stroke	1.2 (14)	2.4 (54)	0.02
Myocardial infarction	0.4 (5)	0.4 (9)	0.88
Major bleeding^	3.3 (38)	5.2 (117)	0.013
Vascular complication	3.0 (35)	4.8 (109)	0.014
New atrial fibrillation	1.9 (22)	5.0 (113)	<0.001
New pacemaker	3.0 (34)	10.9 (246)	<0.001
Coronary obstruction	0.6 (7)	0.4 (9)	0.37
Device embolisation	0.5 (6)	0.4 (7)	0.34
Device capture or retrieval	1.1 (13)	0.4 (9)	0.012
Perforation	0.3 (3)	0.6 (13)	0.20
Aortic dissection	0.1 (1)	0.2 (5)	0.38
Annular rupture	0	0.1 (3)	0.22
Conversion to open-heart surgery	0.2 (2)	0.4 (9)	0.28
Cardiopulmonary bypass	1.0 (11)	1.3 (29)	0.40
Aortic valve reintervention	0.3 (3)	0.6 (13)	0.20

^ According to VARC definition

Mortality, stroke and frequency of in-hospital outcomes were similar in patients with different surgical prosthesis failure modes. Mortality rates were higher in patients with small surgical valves, but there was no statistically significant difference in mortality based the valve size used.

30-day and 1-year outcomes in ViV-TAVI and matched NV-TAVI patients

	Unadjusted HR (95% CI) p value	**Adjusted HR (95% CI) P value**
All-cause mortality		
30-days	0.59 (0.41-0.86), p=0.007	0.50 (0.30-0.84), p<0.01
1-year^	0.53 (0.44-0.63) p<0.001	0.65 (0.51-0.84), p<0.01
Stroke		

30-days	0.58 (0.36-0.93), p=0.025	0.56 (0.30-1.04), p=0.06
1-year	0.61 (0.42-0.87) p=0.007	0.78 (0.47-1.29), p=0.34
Aortic valve reintervention		
30-days	0.65 (0.27-1.56), p=0.339	0.33 (0.09-1.15), p=0.08
1-year	1.1 (0.59-2.04) p=0.77	0.52 (0.20-1.33), p=0.17
Heart failure hospitalisations		
30 days	0.52 (0.35-0.77), p=0.77	0.60 (0.35-1.02), p=0.06
1-year	0.59 (0.47-0.74) p<0.001	0.68 (0.50-0.94), p=0.02

^ 1-year mortality was lower in the VIV-TAVI group compared to NV-TAVI group in younger (<80 years old) as well as older patients (>80 years old).

Abbreviations used: AVG, aortic valve gradient; CI, confidence interval; HR, hazard ratio; NR, not reported; NV-TAVI, native valve transcatheter aortic valve implantation; VARC, Valve Academic Research Consortium; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.

Study 5 Dvir D (2014)

Details

Study type	**Case series (retrospective and prospective data)** **Valve-in-Valve International Data (VIVID) Register (independent register by experts).**
Country	Europe, North America, Australia, New Zealand and the Middle East (55 centres)
Recruitment period	2007 to 2013
Study population and number	n=**459** Bioprosthesis mode of failure (according to ASE): stenosis (39.4%, 181/459), regurgitation (30.3%, 139/459), or combined stenosis and regurgitation (30%, 139/459). Type of degenerated bioprosthesis: stented 79.7% (366/459), stentless 20.3% (93/459). Surgical valve size:<21mm: 29.5% (133/459),>21 and<25 mm: 38.3% (176/459),>25 mm:30.3% (139/459), unknown 2.4% (11/459) Stenosis group had more stented valves (95% versus 60.4% versus 78.4%) and more small valves (37% versus 20.9% versus 26.6%, p=.005). >1 previous SAVR, % (n): 13.5% (62/459) Logistic EuroSCORE: 29% STS score: 10 % Mean time from last SAVR-VIV: 9 years
Age and sex	Age: mean 77.6 years Sex: 44% (205/459) female
Patient selection criteria	Patients with failing surgical aortic bioprostheses having valve-in-valve implantation were included. Valve-in-valve procedures performed using other transcatheter devices or implanted in positions other than the aortic valve were not included in the current analyses.
Technique	Technique: ViV-TAVI Devices: balloon and self-expandable valves, CoreValve (n=213) [23, 26, 29, 31 mm] and Edwards SAPIEN (n=246) [20, 23, 26, 29 mm]. Access: transfemoral 58.8% (n=270), transapical 37.3% (n=171), transaxillary 2.8% (n=13), direct aortic 1.1% (n=5).
Follow up	**median 302 days**
Conflict of interest/source of funding	Authors report serving as proctors and consultants for different manufacturers. Some received honoraria and grants.

Analysis

Follow-up issues: Complete follow up.

Other issues: Data were collected retrospectively for cases performed before register initiation and prospectively thereafter. There was no statistically significant difference in STS scores when stratified according to mechanism of failure. Comparative data between the CoreValve and Edwards SAPIEN groups not reported here.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **459**

Procedural echocardiographic outcomes (mean±SD)

	All (n=459)	**Stenosis (n=181)**	**Regurgitation (n=139)**	**Combined (n=139)**	**p value**
Peak aortic valve gradient (mmHg)					
Baseline	60.8±27.4	75.2±23.1	34.3±17.7	64.6±22.8	<.001
30 days	28.3±14.1	32.2±14.7	22.4±11.6	29.1±13.6	<.001
1 year	30±14.7	32.3±14.9	25.2±15.4	32.1±12.5	.005
Mean aortic valve gradient (mmHg)					
Baseline	36.2±18.4	46.4±16.1	18.0±10.1	37.6±14.9	<.001
30 days	15.8±8.9	18.5±9.8	12±6.7	16.1±8.3	<.001
1 year	16.9±9.1	18.3±9.5	13.8±8.9	18.4±8	.001
Aortic valve area (cm^2)					
Baseline	0.95±0.48	0.69±0.21	1.48±0.6	0.91±0.31	<.001
30 days	1.47±0.5	1.37±0.33	1.56±0.51	1.56±0.65	.01
1 year	1.38±±0.42	1.28±0.29	1.51±0.48	1.36±0.45	.01
Mean LVEF %					
Baseline	50.3±13.1	51.7±12.9	49.0±13.1	49.7±13.3	.16
30 days	51.6±11.5	53.7±9.9	48.9±11.6	51.2±12.9	.002
Aortic regurgitation (≥ moderate)^, % (n)					
Baseline	64.5 (296/459)	12.2 (22)	100(139)	97.1 (135)	<.001
30 days	5.4 (25)	2.8 (5)	9.4 (13)	5 (7)	.04

^according to ASE criteria

NYHA functional class

	All (n=459)	**Stenosis (n=181)**	**Regurgitation (n=139)**	**combined (n=139)**	**P value**
Baseline					
I/II	7.8 (35/459)	7.7 (14/181)	7.2 (10/139)	7.9 (11/139)	.97
III/IV	92.6 (424/459)	98 (167/181)	92.8 (129/139)	92.1 (128/139)	.001
30 days					
I/II	926 (313/338)	91.3 (126/138)	94.3 (100/106)	92.6 (87/94)	.83
III/IV	7.4 (25/338)	8.7 (12/138)	5.7 (6/106)	7.4 (7/94)	.83
1 year					
I/II	86.2 (163/189)	84.9 (62/73)	85.2 (46/54)	88.7 (55/62)	.34

Safety

Procedural adverse events % (n)

Ostial coronary obstruction.	2 (more frequent in stenosis group (3.9%; p=.02)
Attempted device retrieval during self-expandable procedures because of device malposition (further details not reported)	10.3 (21/213)
Implantation of a second TAVI valve (because of device malposition)	5.7 (26/459)

Complications at 30 days and 1 year % (n)

All-cause mortality at 30 days	7.6 (35/459)
Cardiovascular deaths	6.5 (30/459)
all-cause mortality at 1 year	16.8 (62/459)
Major stroke^	1.7 (8/459)
Major vascular complication (further details not reported)^	9.2 (42/459)
Major/life-threatening bleeding	8.1 (37/459)
Acute kidney injury type II/III	7.4 (34/459)
Permanent pacemaker implantation	8.3 (38/459)
Severe patient−prosthesis mismatch (incidence lower in regurgitation group compared to stenosis and combined group (19.3% versus 36.1 and 36.4%; p=.03).	31.8

^ According to VARC definition

Patients in the stenosis group had a higher 30-day mortality rate (10.5% versus 4.3% in the regurgitation group and 7.2% in the combined group; p=.04).

1-year mortality was higher among patients having transapical procedures, those with STS scores higher than 20%, and with a baseline LVEF of less than 45%.

III/IV	13.8 (26/189)	15.1 (11/73)	14.8 (8/54)	11.3 (7/62)	.34

Survival (Kaplan–Meier survival curve)

The overall 1-year survival rate was 83.2%

(95% CI 80.8% –84.7%; 62 deaths; 228 survivors).

Patients in the stenosis group had worse 1-year survival (76.6%; 95% CI, 68.9-83.1%; 34 deaths, 86 survivors) in comparison with the regurgitation group (91.2%; 95% CI, 85.7-96.7%; 10 deaths, 76 survivors) and the combined group 83.9%; 95% CI, 76.8-91%; 18 deaths, 66 survivors; p=.01).

Patients with small valves had worse 1-year survival after VIV procedure (74.8%; 95% CI 66.2-83.4%; 27 deaths; 57 survivors) versus with intermediate sized valves (81.8%; 95% CI, 75.3-88.3%; 26 deaths; 92 survivors) or with large valves (93.3%; 95% CI, 85.7-96.7%; 7 deaths; 73 survivors; p=0.001).

Factors associated with mortality within 1 year included having small surgical bioprosthesis (≤21mm; hazard ratio, 2.04; 95% CI, 1.14-3.67; p=.02) and baseline stenosis (versus regurgitation, hazard ratio, 3.07; 95% CI, 1.33-7.08; p=.008).

Abbreviations used: ASE, American Society of Echocardiography; AR, aortic regurgitation; CI, confidence interval; EuroSCORE, European System for CARDIAC Operative Risk Evaluation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association; PPM, patient–prosthesis mismatch; STS, Society of Thoracic Surgeons; SD, standard deviation; TEE, transoesophageal echocardiogram; TTE, transthoracic echocardiogram; VARC, Valve Academic Research Consortium; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.

Study 6 Webb JG D (2017)

Details

Study type	**Case series** **PARTNER 2 (placement of aortic transcatheter valves) ViV Registry**
Country	North America (34 sites)
Recruitment period	2012 to 2014
Study population and number	n=**365 patients at high risk having ViV-TAVI within degenerated aortic surgical bioprostheses** Bioprosthesis mode of failure (according to ASE): stenosis (55.2%, 197/357), regurgitation (23.5%, 84/357), or combined stenosis and regurgitation (21.3%, 76/357). Type of degenerated bioprosthesis: stented 92.3% (337/365), stentless 6.0% (22/365), unknown 1.6% (6/365). Surgical valve size:<21mm: 26.8% (96/354), 23-25 mm: 60.4% (218/361),>25 mm:12.2% (44/361), Stenosis group had more stented valves (95% versus 60.4% versus 78.4%) and more small valves (37% versus 20.9% versus 26.6%, p=.005). Logistic EuroSCORE: 12.3±9.8% STS score: 9.1±4.7% % NYHA functional class III or IV: 90.1%; left ventricular ejection fraction (LVEF): 48.6±13.2% Surgical bioprosthesis age:<5 years (6.8% [14/205]), 5 to 10 years (26.8% [55/205),>10 years (66.3% [136/205])
Age and sex	Age: mean 78.9 years; sex: 64% male
Patient selection criteria	Inclusion criteria: patients with symptomatic degeneration of surgical aortic bioprostheses at high risk (>50% major morbidity or mortality) for reoperative surgery enrolled in the multicentre PARTNER 2 VIV trial and included in initial nested registry (n=92) and additional patients enrolled in a continued access registry (n=269). Exclusion criteria: bioprosthetic valve with a labelled size<21 mm, more than mild paravalvular regurgitation, LVEF<20%, or an estimated life expectancy of<2 years.
Technique	Technique: ViV-TAVI Anaesthesia: sedation 12%, general anaesthesia 88% Devices: balloon-expandable THV valves Sapien XT 23 (69%) and 26 mm (31%) were used. Access: transfemoral 75.4% (273/362), transapical 24% (87/362), transaortic 0.6% (2/362).
Follow up	**30 days and 1 year**
Conflict of interest/source of funding	Company sponsored study (sponsor had no role in data analysis). Authors received grants or consulting fees from companies.

Analysis

Follow-up issues: limited follow up, at 1 year no patients were lost to follow up.

Study issues: large cohort study (registry data), data were collected at baseline and follow-up time points. A clinical events committee adjudicated all clinical events and safety monitoring board reviewed all adverse events. Primary outcome was all-cause mortality at 1 year. Patients with larger or smaller surgical prostheses were excluded from the trial.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **459**

Echocardiographic outcomes, mean (95% CI)

	Baseline (n=353)	**1 year (n=232)**	**Difference (baseline to 1 year)**	**P value**
EOA, cm^2	0.93 (95% CI 0.89–0.98)	1.16 (1.11–1.21)	0.23	<0.0001
EOA index, cm^2/m^2	0.49 (0.47–0.51)	0.60 (0.57–0.63)	0.11	<0.0001
Mean gradient, mmHg	35.0 (33.7–36.2)	17.6 (16.2–19.1)	-17.4	<0.0001
Aortic regurgitation % (n)				
None	11.7 (29/247)	63.2 (67/106)		
Trace	18.6 (46/247)	30.2 (32/106)		
Mild	25.9 (64/247)	4.7 (5/106)		
Moderate	27.1 (67/247)	1.9 (2/106)		
Severe	16.6 (41/247)	0		

When 30-day and 1-year echocardiographic data were compared, no statistically significant differences in mean EOA (1.13 cm^2 versus 1.16 cm^2, p=0.30) or mean gradient (17.7 mmHg versus 17.6 mmHg; p=0.90) were seen.

Patients with stenotic bioprosthetic failure had higher 1-year mean gradient (18.9 mmHg versus 16.0 mmHg; p<0.0001) and lower indexed EOA (0.57 versus 0.65 cm^2/m^2; p<0.0001) than those with regurgitant or mixed failure and had greater proportional changes in both mean gradient and EOA at 1 year.

NYHA functional class

	Baseline	**30 days**	**1 year**
I	0	54	56.1
II	9.9	35.3	33.1
III	62.5	9.5	9.3
IV	9.9	1.2	1.5

Quality of life

The mean overall summary KCCQ score was 43.0 (least squares: 40.7 to 45.3) at baseline, increasing to 70.6 (68.2 to 72.9) at 30 days and 76.2 (73.5 to 78.8) at 1 year (p<0.0001); and mean 6-min walk test distance increased from 163.7m (least squares: 145.8 to 181.7) at baseline to 229.3 m (211.2 to 247.5 m) at 30 days and 248.0 m (226.9 to 269.1 m) at 1 year (p<0.0001). No differences in KCCQ scores were seen when patients were stratified according to bioprosthesis size or residual gradient.

Safety

Complications at 30 days and 1 year % (n)

	30 days % (n)	**1 year % (n)**
All-cause mortality^	2.7 (10)	12.4 (43)
Cardiovascular deaths	2.5 (9)	9 (31)
Myocardial infarction	1.4 (5)	1.4 (5)
All Stroke	2.7 (10)	4.5 (16)
Disabling stroke	2.2	
Coronary occlusion	0.8 (3)	
Major vascular complications	4.1 (15))	4.4 (16)
All vascular complications	7.4 (27)	7.7 (28)
Acute kidney injury type I/II/III	7.5 (27)	8.7 (31)
Permanent pacemaker implantation	1.9 (7)	2.6 (9)
Major bleeding	20.8 (76)	23.2 (84)
Rehospitalisation	5.9 (21)	15.9 (53)
Moderate paravalvular aortic regurgitation	NA	1.0 (1/105)
Mild paravalvular regurgitation	NA	4.8 (5/105)
Severe PPM (IEOA<0.65cm2/m2)*	58.4%*	
Conversion to surgery	<1%	

^ Substantially lower mortality was observed in continued access patients than in those in the initial registry (9.8% versus 19.8%; p=0.006; HR 2.29 [95% CI 1.25, 4.18]). Increased mortality was seen in patients with an elevated (>20 mmHg) post-mean gradient (16.7% versus 7.7%, respectively; p=0.01; HR 2.27 [95% CI 1.16, 4.46]).

No increased mortality was observed in patients stratified according to mode of valve failure, access route, 21-mm surgical valves (p=0.31), or severe PPM (p=0.86) and multivariate analyses adjusted for these variables and baseline STS risk score revealed no statistically significant associations with 1-year mortality.

*statistically significant difference was seen between 21mm valves and larger valves (69.5% versus 55%, p=0.03).

Abbreviations used: ASE, American Society of Echocardiography; CI, confidence interval; EuroSCORE, European System for CARDIAC Operative Risk Evaluation; EOA, effective orifice area; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association; PPM, patient–prosthesis mismatch; STS, Society of Thoracic Surgeons; VARC, Valve Academic Research Consortium; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.

Study 7 Deeb GM (2017)

Details

Study type	**Case series (prospective data)** **CoreValve U.S. Expanded Use Study**
Country	North America (34 sites)
Recruitment period	2013 to 2015
Study population and number	n=**227 patients at high risk with surgical valve failure having self-expanding ViV-TAVI** Bioprosthesis mode of failure (according to ASE): stenosis (56.4%), regurgitation (22%), or combined stenosis and regurgitation (21.6%). Type of degenerated bioprosthesis: stented 81.9% (186/227), stentless 11.5% (26/211) and homograft 6.6% (15/211) Failed surgical valve size: most were smaller stented surgical valves (<23 mm in diameter Logistic EuroSCORE: 23.7±16.5%; STS score: 9.0±6.7% NYHA functional class III or IV: 86.8% Surgical bioprosthesis age:<5 years (11.4% [24/211]), 5 to 10 years (32.7% [69/211]),>10 years (55.9% [118/211]); average surgical valve duration 10.2 years.
Age and sex	Age: mean 76.7 years; sex: 63% male
Patient selection criteria	Inclusion criteria: patients at high risk (defined as a 50% or greater risk for mortality or irreversible morbidity at 30 days) with symptomatic surgical valve failure deemed unsuitable for reoperation determined by 2 clinical site cardiac surgeons and confirmed by a National Screening Committee. Exclusion criteria: evidence of myocardial infarction, percutaneous coronary intervention 30 days before the procedure, blood dyscrasias, coronary artery disease needing revascularisation, cardiogenic shock, severe ventricular dysfunction, recent TIA or cerebrovascular accident, ongoing sepsis, endocarditis, active GI bleeding, hypersensitivity or contraindication to anticoagulation, or anatomical and vascular problems (such as native annulus or surgical bioprosthesis size<17 or>29mm, heart valves in mitral or pulmonary position, mitral stenosis, mixed aortic valve disease).
Technique	Technique: ViV-TAVI Anaesthesia: sedation 12%, general anaesthesia 88% Devices: self-expanding THV valves (23, 26, 29 or 31mm diameter Medtronic CoreValve bioprosthesis) were used. Access: iliofemoral 75.4% (273/362), axillary 24% (87/362), direct aortic 0.6% (2/362). Implantation depth: 3 to 4mm below the bioprosthetic valve annulus.
Follow up	**30 days and 1 year**
Conflict of interest/source of funding	Company sponsored study (company employees with data analysis and overall study management). Authors received grants, research support or provided assistance consulting fees from companies.

Analysis

Follow-up issues: at 1-year follow up, 13 patients died and 3 withdrew from study.

Other issues: large prospective non-randomised study. Primary endpoints (mortality or major stroke at 1 year) were defined using the Valve Academic Research Consortium-1 criteria. Symptom status was assessed using NYHA functional classification system. Quality of life was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score. An independent core laboratory evaluated post-procedural echocardiograms for valve haemodynamics. Additional analyses were also done to evaluate the predictors of residual mean valve gradient after ViV-TAVI.

Population issues: 97% of patients had congestive heart failure.

Other issues: authors attribute low complication rates to careful pre-procedural screening, including computed tomography angiography.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **227**

Procedure outcomes

	% (n)
Technical success	99 (225/227)
Device success	93.3 (210/225)
Device failure	6.7 (15/227)*
Procedure success	90.2 (203/227)
Procedure failure	9.8 (22/227)^

*11 patients had more than 1 bioprosthesis implanted, 3 had isolated vascular access complications and 1 had multiple complications (malposition, vascular access complication and more than 1 device implanted).

^15 were because of device failure and 7 had major adverse cardiovascular and cerebrovascular events.

Echocardiographic outcomes (mean±SD)

	Baseline	**30 days**	**1 year**	**P value**
Mean aortic gradient, mmHg	37.7± 18.1 (n=224)	17.0 ± 8.8 (n=200)	16.6 ± 8.9 (n=119)	<0.001
EOA, cm^2	1.02 ± 0.61 (n=216)	1.41 ± 0.65 (n=173)	1.41 ± 0.62 (n=93)	<0.001
Aortic regurgitation % (n)				
None	NR	68.7 (138)	67.2 (82)	NR
Mild	NR	27.9 (56)	25.4 (31)	NR
Moderate	NR	3.5 (7)	7.4 (9)	NR
Severe	NR	0	0	NR

Impact of mode of surgical valve failure, degree of PPM and valve size on MVG

The mean aortic valve gradient was statistically significantly higher with smaller valve size at discharge (p<0.001) and 1 month (p=0.01) but not statistically significant at 12 months. Severe PPM and stenosis as a modality of failure were associated with statistically significantly higher gradients at 1 months and 6 months after the procedure (p=0.004, p=0.002) but not statistically significant at 12 months (p=0.13, p=0.28).

Subgroup analysis showed that the percentage of patients with mean gradients>20 mmHg at 1 month is elevated when stenosis is combined with either small surgical valves or severe PPM, and when small surgical valves are combined with severe PPM.

Impact of 1-month MVG (<20mmHg or>20mmHg) on all-cause mortality and a composite outcome of mortality, rehospitalisation, and reintervention

There was no statistically significant difference in the 1-year mortality rate between patients with 1-month MVG of<20mmHg

Safety

Complications at 30 days and 1 year % (n)

	30 days % (n=227)	**1 year % (n=186)**
All-cause mortality	**2.2 (5)**	**14.6 (26)**
Cardiovascular deaths	1.8 (4)	7.7 (13)
Valve-related deaths^	0	0.7 (1)
Non-cardiovascular deaths	0.5 (1)	7.5 (13)
Neurological events including strokes and TIAs	**2.7 (6)**	**7.9 (13)**
All stroke	0.9 (2)	3.1 (5)
Major stroke	0.4 (1)	1.8 (3)
Minor stroke	0.5 (1)	1.2 (2)
TIA	0.5 (1)	1.9 (3)
Myocardial infarction	0.9 (2)	0.5 (1)
Reintervention (surgical and percutaneous)	0.9 (2)	2.4 (4)
Major adverse cerebrovascular and cardiac events *	**4.4 (10)**	**18.5 (33)**
Major vascular complications (2 patients died)	10.1 (23)	11.3 (21)
Acute kidney injury	4.0 (9)	3.8 (7)
Permanent pacemaker implantation	8.1 (18)	11 (19)
Major bleeding	14.7 (33)	16 (29)
Life-threatening bleeding	6.2 (14)	11.9 (21)
Cardiac perforation (patient died)	0.4 (1)	1.2 (2)
Coronary occlusion (patient died)	0.4 (1)	
Cardiogenic shock	2.2 (5)	2.7 (5)
Cardiac tamponade from aortic dissection (patient died)	0.4 (1)	1.2 (2)
Aortic valve rehospitalisation	3.2 (7)	11.8 (20)
Valve-in-valve implantation	4.4 (10)	NR
Prosthetic valve dysfunction	**7.6 (17)**	**11.4 (20)**
Aortic stenosis	4.9 (11)	8.6 (15)
Moderate aortic regurgitation	3.6 (8)	4.0 (7)

*Major adverse cardiovascular and cerebrovascular event includes all-cause death, myocardial infarction, all stroke, and reintervention.

^Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or or>20mmHg (11.1% versus 13.8%, p=0.64). The impact of 1-month MVG on a composite outcome of mortality, rehospitalisation, and reintervention for any reason except residual AR revealed no statistically significant difference between the 2 groups at 1 year (17.5% versus 21.2% , p=0.58).

NYHA functional class

	Baseline % (n=225)	30 days % (n=209)	6 months % (n=185)	1 year % (n=131)
I	0	58.4	62.7	71.8
II	12.4	32.1	31.9	21.4
III	66.7	9.6	4.9	6.1
IV	20.9	0	0.5	0.8

Quality of life (assessed using KCCQ and represented by KCCQ overall summary score change from baseline)

	Baseline	30 days (n=206)	6 months (n=184)	1 year (n=126)
KCCQ summary score Δ	45	Δ=28.7 (p<0.001)	Δ=30.8 (p<0.001)	Δ=39.9 (p<0.001)

When stratified according to bioprosthesis size, modality of surgical valve failure, residual gradient and degree of predicted PPM, the results show that patients with smaller valves, stenosis as a mode of failure, degree of predicted PPM and a mean valve gradient of more than 20mmHg had a smaller improvement in quality of life up to 6 months but reported no change at 1 year.

implanted valve endocarditis or related to reintervention on the operated valve.

Abbreviations used: ASE, American Society of Echocardiography; AR, aortic regurgitation; CI, confidence interval; EuroSCORE, European System for CARDIAC Operative Risk Evaluation; EOA, effective orifice area; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MVG, mean valve gradient; NR, not reported; NYHA, New York Heart Association; PPM, patient–prosthesis mismatch; STS, Society of Thoracic Surgeons; VARC, Valve Academic Research Consortium; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.

Studies of patients with rescue of suboptimal valve-in-valve implantations

Study 8 Stundl A (2015)

Details

Study type	**Case series (prospective registry)**
Country	Germany (single centre)
Recruitment period	2011 to 2013
Study population and number	n=**226 patients at high risk having TAVI with self-expanding valves and with statistically significant paravalvular leakage (PVL) having balloon post-dilation (BPD; n=85) or valve-in-valve (ViV) implantation (n=16) or no corrective measure (n=125)** PVL (according to VARC-2 criteria): no aortic regurgitation [AR] 20.4% (46/226), mild AR (36.7% (83/226), moderate AR 30.5% (69/226), severe AR 12.4% (28/226) Logistic EuroSCORE II: median 5.9% (range 3.8 to 10.8) STS score: 6.8% (4.4 to10.7)
Age and sex	age: mean 81.4 years; sex: 54.4% (123/226) male
Patient selection criteria	Patients with an increased risk for SAVR having TAVI with self-expanding CoreValve prosthesis were included in the registry.
Technique	Technique: All TAVI procedures were performed with biplane fluoroscopy under conscious sedation. Access: transfemoral.97% (219/226), trans-subclavian 0.9% (2/226), and transaortic 2.2% (5/226) Devices: self-expanding THV valves (23, 26, 29 or 31mm diameter Medtronic CoreValve bioprosthesis) were used. In patients with proper implantation depth of the valve but suboptimal frame expansion, BPD was done to obtain a better expansion of the prosthesis stent frame and a better sealing of the paravalvular space. In case of too shallow or too deep positioning of the valve or when BPD did not improve PVL, ViV implantation was considered. The procedure time was longer in patients having ViV-TAVI.
Follow up	**30 days and 1 year**
Conflict of interest/source of funding	4 authors received research grants and speaker honoraria from Medtronic and Edwards Lifesciences.

Analysis

Other issues: small single centre study, angiography and the AR index were used to evaluate the severity of PVL before and after corrective measures in patients suffering from moderate PVL. The severity of PVL was defined according to the VARC-2 criteria. In patients with moderate PVL and an AR index<25, PVL was evaluated by echocardiography to interpret the cause of PVL.

Population issues: Patients with the need for BPD were statistically significantly older, had higher STS scores. ViV implantation and BPD patients had smaller aortic valve areas (AVAs) and higher mean pressure gradients than patients without the need for corrective measures.

Other issues: there was no statistically significant difference in the rate of pre-dilatation, prosthesis size, annulus dimensions, and cover index between the BPD and ViV-TAVI groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **BPD (N=85) versus ViV-TAVI (n=16) versus no corrective measure (n=125)**

Change in AR index in patients with moderate paravalvular leakage (PVL)

	AR index^ before	**AR index^ after**	**P value**
BPD	19.1±11.0	25.9±5.8	<0.001
ViV-TAVI	17.6±6.4	29.5±9.1	0.008

^AR index: aortic regurgitation index calculated as ratio of the end-diastolic transvalvular gradient between diastolic blood pressure (RRdia) in the aorta and LVEDP to systolic blood pressure (RRsys) in the aorta: ([RRdia–LVEDP]/RRsys)×100.

Safety

Adverse events

	All patients % (n=226)	**No correction % (n=125)**	**BPD % (n=85)**	**ViV-TAVI % (n=16)**	**P value**
30-day mortality	5.3 (12)	4.8 (6)	4.7 (4)	12.5 (2)	0.41
1-year mortality	20.4 (46)	21.6 (27)	17.6 (15)	25 (4)	0.69
Stroke	2.2 (5)	2.4 (3)	2.4 (2)	0	0.82
Myocardial infarction	0.9 (2)	0.8 (1)	1.2 (1)	0	0.89
Major vascular complications	8.4 (19)	9.6 (12)	5.9 (5)	12.5 (2)	0.53
Pacemaker implantation	14.2 (32)	16 (20)	11.8 (10)	12.5 (2)	0.63
Moderate paravalvular leak*	6.2 (14)	1.6 (2)	11.6 (10)	12.5 (2)	0.007
Residual AR index<25	29.2 (66)	21.6 (27)	40 (34)	31.3 (5)	0.02

*In 86% (87/101 patients) with moderate PVL, PVL reduction of>1 degree was noted.

Abbreviations used: AR index, aortic regurgitation index; BPD, balloon post-dilatation; EuroSCORE, European System for CARDIAC Operative Risk Evaluation; PVL, paravalvular leak; STS, Society of Thoracic Surgeons; VARC, Valve Academic Research Consortium; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.

Study 9 Ussia GP (2011)

Details

Study type	**Comparative case series** (prospective study) **Italian CoreValve Register**
Country	Italy (14 centres)
Recruitment period	Not reported
Study population and number	Patients having TAVI and those with severe paraprosthetic leaks (PPL) because of malposition and having a second prosthesis implanted inside the first one. n=**663 (24 ViV [3.6%] versus 639 TAVI)** Device malposition in patients having ViV: too low deployment in left ventricle in 75% (n=18/24); high deployment above annulus in 25% (n=6/24). Mean logistic EuroSCORE: 23.0 ± 13.7%
Age and sex	Age: ViV group: mean 80.3 years, TAVI group: mean 81.0 years Sex: ViV group: 54.1% (13/24) female, TAVI group: 56% (358/639) female
Patient selection criteria	not reported
Technique	Technique: ViV versus TAVI technique Route of implantation: ViV Group: (transfemoral 90.4% [23/24] or trans-subclavian 9.6% [1/24] TAVI group: (transfemoral 90.1% [576/639] or trans-subclavian 9.9% [63/639] Device used: 18-F Core ReValving System (CRS) (Medtronic) ViV group: CRS size: 26mm, 62.5% (15/24) CRS size: 29mm, 37.5% (9/24) TAVI group: CRS size: 26mm, 59.3% (379/639) CRS size: 29mm, 40.7% (260/639) Mean annulus diameter: ViV 23.6 ± 2.7mm; TAVI 22.1 ± 2.12 mm; p=0.010; measured by TEE or TTE). Prosthesis was managed with balloon dilation in 54% (13/24) patients without any damage to leaflets or aortic root.
Follow up	**10.5 months (median; range 6.5 to 16.7 months)**
Conflict of interest/source of funding	6 authors are proctors for the manufacturer (Medtronic Incorporation).

Analysis

Follow-up issues: No loss to follow up reported.

Population issues: No statistically significant difference in baseline clinical characteristics between patients in the ViV group and those in the TAVI group.

Other issues: The authors highlight that it is unclear if the presence of 2 valves could impact on the long-term durability of the prosthesis.
Authors suggest that high success rate might be because of increasing operator familiarity and confidence in device.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **663 (24 ViV versus639 TAVI)**

Procedural success

	ViV group % (n=24)	TAVI group % (n=639)	p valve
Procedural success*	100	97.9	0.616
30-day survival	100	94.4	not reported
1-year survival	95.5	86.3	not reported

* Defined as device deployment with fall of transaortic peak-to-peak gradient, without any periprocedural major adverse cardiovascular and cerebrovascular event within 24 hours of prosthesis implantation.

Functional outcome (NHYA class)

NHYA class III/IV	ViV % (n=24)	TAVI % (n=639)	p value
Baseline	79.2 (19/24)	64.9 (415/639)	0.486
Discharge	0	2.0	0.446
30 days	0	5.6	0.890
1 year	4.1	4.7	0.671

Actual numbers followed up not reported

Echocardiographic outcomes

	ViV (n=24)	TAVI (n=639)	p value
Mean transaortic gradient (mmHg)			
-baseline	45.4 ± 14.8	52.0 ± 17.1	0.0062
-1 year	10.5 ± 5.2	10.1 ± 4.2	0.838
Central aortic regurgitation grade 3+ or 4+			
-baseline	8.3% (2/24)	5.1% (33/639)	0.365
-1year	No cases	No cases	
Paraprosthetic leak grade 2+ or more			
-1 year	4.2% (1/24)	11.7% (26/639)	0.675

Reported mean and SD unless otherwise noted.

Safety

Procedural complications

Complication	ViV % (n=24)	TAVI % (n=639)	p value
Intraprocedural mortality	0	0.9 (6/639)	0.801
Intraprocedural major adverse cerebrovascular and cardiac events *	0	2.8 (18/639)	0.510
Major access site complications^	4.2 (1/24)	3.7 (12/639)	0.384
Cardiac tamponade	0	1.2 (8/639)	0.743

* Defined as the composite of death resulting from any cause, myocardial infarction, stroke, or conversion to open-heart surgery.

^ Defined as vascular rupture with fatal bleeding or need for urgent vascular surgery or transcatheter repair.

Mortality at 30 days and other major adverse events

Complication	ViV % (n=24)	TAVI % (n=639)	p value
Mortality (any cause)	0	5.6	0.238
Major adverse cerebrovascular and cardiac events	0	7.0	0.185

Mortality at 1 year and other major adverse events

Complication	ViV % (n=24)	TAVI % (n=639)	p value
Major adverse cerebrovascular and cardiac events	4.5	14.1	0.158
Mortality	4.5	13.7	0.230
Structural valve deterioration	0		
New onset of regurgitation (central or PPL)	0		
Impairment of anterior mitral leaflet	0		
Impingement on the coronary ostia	0		
Embolisation	0		
Thrombosis	0		

Pacemaker implantation

Pacemaker implantation	ViV % (n=24)	TAVI % (n=639)	p value
-baseline	4.2% (1/24)	6.4% (41/639)	0.542
-30 days	33.3%	14.4%	0.020

Abbreviations used: EuroSCORE, European System for CARDIAC Operative Risk Evaluation; PPL, paraprosthetic leak; STS, Society of Thoracic Surgeons; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.

Study 10 Makkar RR (2013)

Details

Study type	**Comparative case series (retrospective)**
Country	**USA and Canada**
Recruitment period	2011 to 2013
Study population and number	Patients having TAVI in the PARTNER RCT (cohorts A with high surgical risk and B with inoperable conditions) and prospective ViV nested registers. **n=2,554** **2.47% (63/2,554) had ViV and 1.01% (26/2,554) had transcatheter valve embolisation (TVE) after TAVI** **VIV versus single TAVI (n=63 versus 2,491)**
Age and sex	Age: mean 84.46 years Sex: VIV 81% male, TVE 76.9% male
Patient selection criteria	Patient inclusion criteria: patients with statistically significant aortic regurgitation often because of not only malpositioning but also leaflet dysfunction. Logistic EuroSCORE: 26.49% STS score: 11.49%
Technique	Technique: patients had TAVI (with first generation Edwards SAPIEN, 23mm or 26mm) with TEE and fluoroscopy guidance. VIV group: a second valve of same size was implanted within the first valve as a 'rescue' option. Indication: statistically significant post AR in 97% (61/63) cases. Transvalvular AR in 50.8% (31/63) Paravalvular AR in 36.1% (22/63) Mixed AR in 13.1% (8/63) 88.9% [56/63] had immediately, 2 after surgical closure in transapical cases, 5 on postoperative days 1,3,16 and at 2 and 4 months. Causes of AR: 33 because of leaflet malfunction, 25 malpositioning, 3 unclear causes. Main causes: technical and anatomical (malpositioning (19%), annulus/aortic valvular complex anatomy (15%), pacing failure (11%). 27% cause unknown). Direction of embolisation: aortic in 50% (13/26) and ventricular in 50% (13/26). 61.5% (16/26) had VIV, 8 had SAVR, 2 no further interventions. Annulus diameter: TVE 2.04 versus no TVE 1.92 cm , p=0.004
Follow up	**1 year**
Conflict of interest/source of funding	None.

Analysis

Population issues: Data were dichotomised for those with and without VIV or TVE.
Device embolisation defined according to VARC criteria: occurring when the 'valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus'.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **63 ViV versus 2,491 TAVI**

26 TVE versus 2,528 no TVE

Outcomes of VIV

VIV group was associated with longer procedure and fluoroscopy times, frequent need for haemodynamic support, increased radiation exposure, contrast use, and larger total CK enzyme than TAVI group.

There were no statistically significant differences in aortic valve area or gradients (10.4 ± 4.5 mmHg versus 10.7 ± 5.0 mmHg, p=0.70) acutely or at follow up in VIV group compared with TAVI group. Post paravalvular, transvalvular and total AR and NYHA status was similar between both the groups.

Impact of VIV on outcomes

ViV was an independent predictor of 1-year cardiovascular mortality (HR: 1.86, 95% confidence interval [CI] 1.03 to 3.38, p=0.041), with a non-significant trend towards greater all-cause mortality (HR: 1.43, 95% CI 0.88 to 2.33, p=0.15).

Safety

30-day outcomes-VIV

	VIV % (n=63)	**TAVI % (n=2,491)**	**p value**
All cause	9.6 (6/63)	5.9 (148/2,491)	0.27
Cardiovascular	8 (5/63)	4.2 (104/2,491)	0.16
Stroke or TIA	4.8 (3/63)	3.8 (93/2,491)	0.68
Myocardial infarction	0	0.8 (20/2,491)	0.47
Open AVR	0	0.6 (14/2,491)	0.55
Vascular complication	9.6 (6/63)	13.2 (327/2,491)	0.39
Pacemaker	11.2 (7/63)	5.4 (133/2,491)	0.05
Renal failure	3.2 (2/63)	2.9 (70/2,491)	0.89
Bradyarrhythmic event	12.8 (8/63)	6.5 (159/2,491)	0.05

At 1 year VIV patients had higher all-cause mortality (33.3% versus 21%, p=0.02), cardiovascular mortality (24.4% versus 9.1%, p=0.0005), and more rehospitalisation (25.5% versus 17.7%, p=0.12) but no statistically significant difference in stroke rates (9.3% versus 4.9%, p=0.17) compared to TAVI patients.

Abbreviations used: AR, aortic regurgitation; CI, confidence interval; EuroSCORE, European System for CARDIAC Operative Risk Evaluation; HR, hazard ratio; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack; TVE, transcatheter valve embolisation; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation;.

Study 11 Kempfert J (2011)

Details

Study type	**Case series**
Country	Germany
Recruitment period	2006-10
Study population and number	High-risk elderly patients who had TA-TAVI and a second rescue bailout prosthesis for malposition valves. n=**15 (out of 305 TAVI procedures)** Failure mechanisms: 'too low' initial valve position (n=7), 'dysfunctional leaflets/central park' after initial valve implantation (n=6), ventricular septal defect (VSD) in the left ventricular outflow tract immediately after initial valve implantation (n=2). Mean Logistic EuroSCORE: 45.5 ± 5.4% STS score: 13.5±1.5 NHYA class: 3.1±0.1; LVEF(%):42±3.9
Age and sex	Age: mean 82.5 years, Sex: 46% (7/15) female
Patient selection criteria	not reported
Technique	Technique: ViV (second SAPIEN prosthesis) of same size implanted in a stepwise inflation technique for final positioning within first stent. Size: 23 mm (2/15), 26 mm (12/15), 29 mm (1/15). Annulus diameter 23.3 ± 0.3
Follow up	**6 months**
Conflict of interest/source of funding	None

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr>
<td>
Number of patients analysed: 15
Procedural outcomes
<table>
<tr><td>Successful ViV implantation %</td><td>100</td></tr>
<tr><td>Procedure time (min)</td><td>108.6 ± 10.3</td></tr>
</table>
The second prosthesis solved leaflet dysfunction, sealed the VSD or corrected the initial misplacement in all patients.
Haemodynamic results (mean± standard deviation)
<table>
<tr><td>Mean aortic gradient (mmHg)</td><td>6.4 ± 2.2</td></tr>
<tr><td>Maximal aortic gradient (mmHg)</td><td>13.7 ± 4.3</td></tr>
</table>
</td>
<td>
Complications % (n)
<table>
<tr><td>30-day mortality
1. because of intestinal ischaemia on postoperative day 1 in 1 patient,
2 low output in 2 patients with preoperative EF<35%,
3 sudden cardiac death in 1 patient on day 5)</td><td>26.6 (4/15)</td></tr>
<tr><td>Access related complications (bleeding, rethoracotomy)</td><td>0</td></tr>
<tr><td>Stroke, valve embolisation, annular tear, coronary impingement, aortic dissection</td><td>0</td></tr>
<tr><td>Pacemaker implantation</td><td>0</td></tr>
<tr><td>Conversion to conventional surgery</td><td>0</td></tr>
<tr><td>Paravalvular leak: none/trace</td><td>80 (12/15)</td></tr>
<tr><td>Paravalvular leak 1+</td><td>20 (3/15)</td></tr>
</table>
</td>
</tr>
<tr><td colspan="2">Abbreviations used: EuroSCORE, European System for CARDIAC Operative Risk Evaluation; LVEF, left ventricular ejection fraction; STS, Society of Thoracic Surgeons; ViV-TAVI, valve-in-valve transcatheter aortic valve implantation.</td></tr>
</table>

Validity and generalisability of the studies

- There are no randomised controlled trials comparing ViV-TAVI with redo SAVR for patients at high risk with previously failed aortic bioprostheses.
- Evidence mainly from observational studies and registry data has reported favourable outcomes. Two systematic reviews and meta-analysis comparing VIV-TAVI with redo-SAVR reported similar outcomes. One registry analysis comparing VIV-TAVI with native valve TAVI reported better outcomes in the VIV implantation group.
- Follow up ranged from 1 month to 1 year.
- There may be some overlap of patients in the global valve-in-valve register with those in other registers.
- Grading systems for assessment of aortic regurgitation were not clearly described in the papers.
- It is difficult to assess the morbidity and mortality directly caused by the procedure in people with such severe illness.

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

- Transcatheter aortic valve implantation for aortic stenosis. NICE interventional procedures guidance 586 (2017). Available from https://www.nice.org.uk/guidance/ipg586
- Sutureless aortic valve replacement for aortic stenosis. NICE interventional procedures guidance 624 (2018). Available from https://www.nice.org.uk/guidance/ipg624
- Percutaneous balloon valvuloplasty for fetal critical aortic stenosis. NICE interventional procedures guidance 613 (2018). Available from https://www.nice.org.uk/guidance/ipg613

- Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. NICE interventional procedures guidance 541 (2015). Available from https://www.nice.org.uk/guidance/ipg541
- Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. NICE interventional procedures guidance 436 (2013). Available from https://www.nice.org.uk/guidance/ipg436
- Balloon valvuloplasty for aortic valve stenosis in adults and children. NICE interventional procedures guidance 78 (2004). Available from https://www.nice.org.uk/guidance/ipg78

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist 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 Specialist Advisers, 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. 3 Specialist Advisor Questionnaires for valve-in-valve TAVI for aortic bioprosthetic valve dysfunction were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 2 completed submissions.

Company engagement

A structured information request was sent to 7 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- The devices used in this procedure may use tissue from animals. These valves may not be acceptable for some patients.
- Lack of long-term follow up in the included studies
- There are a number of studies underway:
  - Polish Transcatheter Aortic Valve-in-Valve Implantation (ViV-TAVI) Registry. NCT03361046. Observational multicentre registry; N=150; status: this study is not yet open for participant recruitment. Estimated start date January 2018, completion date: 2024.

  - The PARTNER II Trial: Placement of AoRTic TraNscathetER Valves II - PARTNER II - Nested Registry 3/Valve-in-Valve. NCT03225001. Single group assignment; n=197; this study is ongoing, but not recruiting participants. Study completion date: December 2020

  - NVT ALLEGRA TAVI System TF in Failing Surgical Aortic Bioprosthesis (VIVALL). NCT03287856. Safety and Performance of the NVT ALLEGRA TAVI System TF in Patients With Failed Surgical Aortic Bioprosthesis and Elevated Surgical Risk. Single group assignment; N=30; this study is currently recruiting participants**.** Completion date October 2019.

References

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2. Phan K, Zhao D-F, Wang N et al (2016). Transcatheter valve-in-valve implantation versus reoperative conventional aortic valve replacement: a systematic review. J Thorac Dis 2016; 8 (1):E83-E93.
3. Chen H-L, Kun L (2016). Clinical outcomes for transcatheter valve-in-valve in treating surgical bioprosthetic dysfunction: A meta-analysis. International Journal of Cardiology 212: 138-141.
4. Tuzcu EM, Kapadia SR et al (2018). Transcatheter aortic valve replacement of failed surgically implanted bioprostheses. The STS/ACC registry. Journal of the American College of Cardiology, 72 (4): 370-82.
5. Dvir D, Webb J, Bleiziffer S et al (2014). Transcatheter Aortic Valve Implantation in failed Bioprosthetic Surgical Valves. The Journal of the American Medical Association. 312, 2:162-170.
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7. Debb GM, Stanley J et al (2017). 1-Year Results in Patients Undergoing Transcatheter Aortic Valve Replacement With Failed Surgical Bioprostheses. JACC: cardiovascular Interventions, 10 (10), 1034-44.
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9. Ussia GP, Barbanti M, Ramondo A et al (2011). The valve-in-valve technique for treatment of aortic bioprosthesis malposition an analysis of incidence and 1-year clinical outcomes from the Italian CoreValve registry. Journal of the American College of Cardiology 57 (9) 1062-1068.2011.
10. Makkar RR, Jilaihawi H, Chakravarty T et al (2013). Determinants and outcomes of acute transcatheter valve-in-valve therapy or embolization: a study of multiple valve implants in the U.S. PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve). Journal of the American College of Cardiology 62 (5) 418-430.2013.
11. Kempfert J, Rastan AJ, Schuler G et al (2011). A second prosthesis as a procedural rescue option in trans-apical aortic valve implantation. European Journal of Cardio-Thoracic Surgery 40 (1) 56-60.2011.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	27/02/2019	Issue 3 of 12, March 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	27/02/2019	Issue 3 of 12, March 2019
HTA (CRD)	27/02/2019	n/a
MEDLINE (Ovid)	27/02/2019	1946 to February 26, 2019
MEDLINE In-Process (Ovid) & MEDLINE Epubs ahead of print (Ovid)	27/02/2019	1946 to February 26, 2019
EMBASE (Ovid)	27/02/2019	1974 to 2019 Week 08
BLIC	27/02/2019	n/a

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

1 Aortic Valve/ab [Abnormalities]

2 Aortic Valve Stenosis/

3 Aortic Valve Insufficiency/

4 (aort* adj4 valve* adj4 (stenos* or insufficien* or incompeten* or regurgitat* or disease* or dysfunct* or malfunct* or degenerat* or position*)).tw.

5 or/1-4

6 Aortic Valve/

7 (aort* adj1 valve*).tw.

8 heart valve prosthesis implantation/

9 bioprosthesis/

10 or/6-9

11 prosthesis failure/

12 (fail* or dysfunction* or degenerat*).tw.

13 11 or 12

14 10 and 13

15 ("valve-in valve" or valve-in-valve).tw.

16 VIV.tw.

17 (minimal* adj4 invasive adj4 reoperat*).tw.

18 ((heart or aort*) adj valv* adj (reoperat* or repeat*)).tw.

19 or/15-18

20 Transcatheter Aortic Valve Replacement/

21 transcatheter*.tw.

22 (TAVI or TAVR).tw.

23 corevalve.tw.

24 (edwards adj4 (sapien or ascendra)).tw.

25 (balloon adj4 expandable adj4 Cribier adj4 Edwards).tw.

26 (LOTUS adj4 edge).tw.

27 PORTICO.tw.

28 JENAVALVE.tw.

29 or/20-28

30 19 and 29

31 5 and 30

32 14 and 30

33 31 or 32

34 animals/ not humans/

35 33 not 34

36 (20140529* or 2014053* or 201406* or 201407* or 201408*or 201409* or 20141* or 2015* or 2016* or 2017*).ed. (3386591) (201712* or 2018*).ed. (201808* or 201809* or 20181* or 2019*).ed.

37 35 and 36

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in table 2
Alnasser S, Cheema AN et al (2017). Matched comparison of self-expanding transcatheter heart valves for the treatment of failed aortic surgical bioprosthesis. Circ Cardiovascular Interventions 10: e004392.	Propensity score matched study N=162 Portico valve (n=54) versus CoreValve (n=108). Follow up=1 year	Post implantation, CoreValve was associated with a larger effective orifice area (1.67 versus 1.31 cm2; P=0.001), lower mean gradient (14±7.5 versus 17±7.5 mmHg; P=0.02), and moderate-to-severe aortic insufficiency (4.2% versus 13.7%; P=0.04), compared with Portico. Procedural complications including THV malpositioning, need for a second THV, or coronary obstruction were not statistically significantly different between the 2 groups. Survival and stroke rates at 30 days were similar, but overall mortality at 1 year was higher among patients who had Portico compared with CoreValve (22.6% versus 9.1%; P=0.03).	Comparing different types of THVs for VIV implantations.
Abdel-Wahab M, Simonato M et al (2018). Clinical valve thrombosis after transcatheter aortic valve-in-valve implantation. Circulation: Cardiovascular Interventions (11) 11 e006730	Case series N=300 VIV implantations in viv data registry.	The incidence of clinical valve thrombosis was 7.6% (23/300), diagnosed at a median time of 101 days (range, 21–226). 65% patients (15/23) presented with worsening symptoms and 91% (21/23) with elevated transvalvular mean gradient. The mean gradient at the time of diagnosis (median 39 mm Hg; range, 30–44) was significantly higher than immediately post-ViV (13 mm Hg; range, 8–20.5; *P*<0.001) and was significantly reduced after oral anticoagulation therapy (17.5 mm Hg; range, 11–20.5; *P*<0.001). There were no deaths or strokes related to valve thrombosis. Factors associated with valve thrombosis were oral anticoagulation (odds ratio [95% confidence limits]: 0.067	Lager studies included in table 2.

		[0.008–0.543], *P*=0.011), surgical valve true internal diameter indexed to body surface area (0.537 [0.331–0.873], *P*=0.012), and Mosaic or Hancock II stented porcine bioprostheses (4.01 [1.287–12.485], *P*=0.017). A higher incidence was observed after treatment of stented surgical valve types, suggesting a specific adjustment of the adjunctive antithrombotic therapy in this subset of ViV patients.	
Attias D, Nejjari M et al (2018). How to treat severe symptomatic structural valve deterioration of aortic surgical bioprosthesis: Transcatheter valve-in-valve implantation or redo valve surgery? European Journal of Cardiothoracic Surgery (54) 6 1-9.	Review	The aim of this review is to provide a framework for individualized optimal treatment strategies in patients with failed aortic surgical bioprosthesis.	Review
Bapat V, Davies W et al (2014).Use of balloon expandable transcatheter valves for valve-in-valve implantation in patients with degenerative stentless aortic bioprostheses: technical considerations and results. The Journal of Thoracic and Cardiovascular Surgery. 148 (3), 917–24.	Prospective case series N=10 patients with failing stentless bioprostheses had ViV Follow up: mean 8.1 months	Technical success achieved in 9 patients. One patient needed immediate placement of a second valve owing to low placement of the first. Two intraoperative complications developed, one patient had immediate repair of a right ventricular perforation from a pacing lead, the other, re-exploration for epicardial bleeding. No deaths occurred. The median length of stay was 8.5 days (range, 3-44).	Larger studies with longer follow included in table 2. Included in systematic review added to table 2 (Phan, 2016).
Bapat V, Attia R et al (2012). Use of transcatheter heart valves for a valve-in-valve implantation in patients with degenerated aortic bioprosthesis: Technical considerations and results. The Journal of Thoracic and Cardiovascular Surgery, 144 (6), 1372–80.	Case series N=23 patients with a failing bioprostheses in the aortic position had ViV-TAVI Follow up: 30 days	Procedural success was 100%, 1 patient with a degenerated homograft needed immediate placement of a second valve because of low placement of the first. The reduction in the mean gradient was 31.2 ± 17.06 mmHg to 9.13 ± 4.9 mmHg. In those patients with predominant aortic regurgitation (9/23), reduction in aortic regurgitation was achieved in all. In-hospital and/or 30-day mortality was 0%.	Larger studies with longer follow included in table 2. Included in systematic review added to table 2 (Chen 2016).
Bedogni F, Laudisa ML, Pizzocri S et al. (2011). Transcatheter valve-in-valve implantation using	Italian Registry 25 patients at high risk with failed	Implantation success rate was 100%. In group A, the peak aortic gradient statistically significantly decreased from	Larger studies with longer follow included in table 2. Included in

Corevalve Revalving System for failed surgical aortic bioprostheses. Jacc: Cardiovascular Interventions 4: 1228–34.	surgical aortic bioprosthesis. Patients/prostheses were divided in type A (mainly stenotic, n=9) and type B (mainly regurgitant, n=16). Technique –ViV-TAVI Follow up: 6 months (mean)	77.6 ± 21.6 mmHg to 34.6 ± 19.4 mmHg (p=0.001). In all but 2 patients in group B, no statistically significant regurgitation was observed post implantation. No patients died during the procedure. At 30 days, there were 3 deaths (12%), 2 myocardial infarctions (8%), and 3 atrioventricular blocks needing pacemaker implantation (12%). At a mean follow up of 6 months, there were another death (survival rate of 84%) and a pacemaker implantation (cumulative incidence of 16%). New York Heart Association functional class improved in all patients to I and II.	systematic review added to table 2 (Phan, 2016)
Buchanan KD, Alraies MC et al (2018). Bioprosthesis leaflet thrombosis following self-expanding valve-in-valve transcatheter aortic valve replacement in patient taking factor Xa inhibitor and warfarin: A case report. Cardiovascular Revascularization Medicine (19) 1 Pt A 29-32.	Case report In an 87-year-old patient a second 29mm valve was placed to abolish paravalvular regurgitation after TAVI.	Routine follow-up computed tomography (CT) imaging showed leaflet thickening and decreased leaflet mobility suggesting valve thrombosis, despite adherence to Factor Xa inhibitor. Transthoracic echocardiogram revealed normal transaortic valve gradients. The patient was transitioned to a vitamin K antagonist and repeat imaging 3months later showed progression of thrombosis to an additional leaflet. The case illustrates the potential increased risk of leaflet thrombosis in patients receiving valve-in-valve TAVR procedures, the superiority of multidetector computed tomography to image subclinical leaflet thrombosis.	Lager studies included in table 2.
Buscaglia A, Tini G et al (2018). Sudden death after valve-in-valve procedure due to delayed coronary obstruction: a case report. Journal of Medical Case Reports [Electronic Resource] (12) 1 247.	Case report A Caucasic 84-year-old woman with degenerated aortic Mitroflow bioprosthesiS had a VIV-TAVI with a CoreValve bioprosthesis.	Few hours later, patient experienced sudden cardiac death. An autopsy showed that Mitroflow prosthesis leaflets were higher than the left main coronary ostium. Fatality was ascribed to left main coronary ostium obstruction because of apposition of the Mitroflow leaflet pushed upward by the late expansion of CoreValve. Coronary artery obstruction is a frequently fatal complication which usually presents just after valve implantation, but, as reported in our case, it may	Lager studies included in table 2.

		also have a delayed presentation. Accurate patient's selection and intraoperative preventive measures can reduce this eventuality.	
Camboni D, Holzamer A et al (2015). Transcatheter valve-in-valve implantation emphasising strategies for coronary protection. The Annals of Thoracic Surgery. 99, 5: 1532–8.	Retrospective case series N=31 patients with degenerated bioprostheses had a VIV procedure.	Procedural success rate was 88%. The left main stem was occluded in 1 patient who had emergent revascularisation. Two patients with a degenerated Mitroflow prosthesis who had a Sapien XT developed post-procedural myocardial ischaemia and deceased on postoperative days 1 and 2, coronary insufficiency associated to the VIV procedure was 10%. The mean gradient decreased statistically significantly from 39.3 ± 14.0 to 16.1 ± 7.2 mmHg (p=0.002). Post-procedural regurgitation was classified as trace in 7 patients (23%) and moderate in 4 patients (13%). The 30-day survival was 77% with a statistically significantly improved NYHA class of 1.79 ± 0.58 (p=0.001).	Larger studies with longer follow included in table 2. Included in systematic review added to table 2 (Phan, Chen 2016).
Castriota F, Nerla R et al (2017). Transcatheter aortic valve-in-valve implantation using Lotus valve for failed surgical bioprostheses. The Annals of Thoracic Surgery 104,2: 638–44.	Case series N=12 patients with degenerated bioprostheses at risk of redo surgery had VIV-TAVI (Lotus valve). Italian VIV registry Follow up: 6 months	Implantation success rate was 92%, in 1 patient the valve was retrieved because of unsatisfactory gradients after valve positioning. In patients with aortic stenosis aortic gradient decreased from 46.7 to 16.6 mmHg (p<0.001). No patients had more than mild aortic regurgitation. Improvement in NYHA function status was seen in all patients (class I to II).	Larger studies with longer follow included in table 2.
Cheung AW, Ye J et al (2018). Aortic Valve-in-Valve in Externally Mounted Bioprosthesis: A Safe Treatment Option for Bioprosthetic Structural Valve Dysfunction. Innovations 13: 171–6.	Retrospective comparative case series N=80 aortic VIV patients with internally (n=61) and externally (n=19) mounted leaflet valves. Follow up: 30 days	Procedural success was achieved in 95%of cases with an overall 30-day mortality of 1.3%. Clinical and procedural outcomes were similar in the both cohorts. Coronary occlusion occurred in 2.5% patients.	Comparison between internally and externally mounted leaflet bioprosthesis.
Conzelmann L, Wurth A et al (2018). Feasibility of transcatheter aortic valve implantation in patients	N=86 patients with coronary height of 6.4mm had TAVI	Coronary-related complications occurred less frequently after TAVI, but once they occurred, they were serious. These TAVI	Larger studies included in table 2.

with coronary heights<7mm: insights from the transcatheter aortic valve implantation Karlsruhe (TAVIK) registry. Eur J Cardiothorac Surg; 54:752–61.	TAVI n=76 VIV-TAVI n=10 Follow up: 1 year	procedures are feasible, with a high procedural success rate, but preoperative planning should be mandatory. In ViV procedures, coronary obstruction occurred in 3, myocardial infarction in 3 patients. The 30-day mortality was reported in 1 patient and follow-up mortality rate increased to 40% (P<0.001; hazard ratio 7.96). Therefore, we do not recommend these procedures.	
Chan PH, Di C, Davies S et al. (2011). Transcatheter aortic valve implantation in degenerate failing aortic homograft root replacements. Journal of the American College of Cardiology 58: 1729–31.	Case series n=5 Follow up ranged from 90 days to 713 days. TAVI with self-expanding prosthesis to treat severe AR because of structural degeneration in a prior homograft aortic root replacement. 26 mm Corevalve (Medtronic)	Device success: 80% At follow up, all patients had marked symptomatic improvement with no more than mild AR. Mean aortic gradient improved from 24.0 ± 16.5 mmHg to 8.2 ± 2.8 mmHg (p=0.07). NHYA functional class- III or IV to I or II. No complications. Short- and medium-term clinical outcomes satisfactory.	Larger studies with longer follow up in table 2.
Chiam PTL, Ewe SH et al (2016). Percutaneous transcatheter aortic valve implantation for degenerated surgical bioprostheses: the first case series in Asia with one-year follow-up. Singapore Medical Journal 57 (7): 401–5.	Case series N=8 patients who had VIV-TAVI for degenerated aortic bioprostheses. Duration to degeneration was 10.2 years.	VIV-TAVI successfully done in all patients. There were no deaths, strokes, or need for a permanent pacemaker at 30 days with 1 non-cardiac mortality at 1 year. All had NHYA functional class improvement. Mean pressure gradients were 20mmHg and 22 mmHg at 30 days and 1 year. Aortic regurgitation of more than mild severity occurred in 1 patient at 30 days and at 1 year 1 patient had mild residual aortic regurgitation.	Larger studies with longer follow included in table 2.
Choi CH, Cheng V et al (2018). A comparison of valve-in-valve transcatheter aortic valve replacement in failed stentless versus stented surgical bioprosthetic aortic valves. Catheterization & Cardiovascular Interventions (27) 27.	Comparative study (retrospective analysis) N=40 VIV-TAVI in failed surgical bioprosthetic valves (8 stented versus 32 stentless valves)	ViV procedure success was 96.9% (31/32) in stentless group and 100% in stented group (8/8). There were no significant differences in all-cause mortality at 30 days between stentless and stented groups (6.9%, 2/31 versus 0%, 0/8, P=0.33) and at 1 year (0%, 0/25 versus 0%, 0/5). In the stentless group, 34.4% (11/32) required a second valve compared to the stented group of 0% (0/8). There was a	Lager studies included in table 2.

		significant difference in the mean aortic gradient at 30-day follow up (12.33 +/- 6.33 mmHg and 22.63 +/- 8.45 mmHg in stentless and stented groups, P<0.05) and at 6-month follow up (9.75 +/- 5.07 mmHg and 24.00 +/- 11.28 mmHg, P<0.05), respectively.	
Cockburn J, Dooley M et al (2017). Transcatheter aortic valve-in-valve treatment of degenerative stentless supra-annular Freedom Solo valves: a single centre experience. Catheterization and Cardiovascular Interventions 89: 438–44.	Case series N=6 patients at high risk with failed supra-annular stentless bioprostheses (5 AS, 1 AR) had VIV-TAVI. Follow up: post implant.	Successful VIV-TAVI was achieved in 67% (4/6) patients. The peak gradient fell from 83 to 38mmHg, no patient had>1 aortic regurgitation.1 patient had a stroke on day 2 and recovered fully. VIV-TAVI was unsuccessful in 2 patients. In 1 patient delivery of the CoreValve was successful but on removal of guide catheter coronary obstruction occurred, needing valve snaring into the aorta. In another patient BAV with simultaneous aortography revealed left main stem occlusion, so the patient had repeat surgery.	Larger studies with longer follow included in table 2.
de Freitas Campos Guimaraes L, Urena M et al (2018). Long-Term Outcomes After Transcatheter Aortic Valve-in-Valve Replacement. Circulation: Cardiovascular Interventions (11) 9 e007038.	n-=116 VIV-TAVI. Balloon- and self-expandable valves were used in 47.9% and 52.1% of patients. Median follow up of 3 years (range, 2-7 years)	30-day mortality was 6.9%. At a median follow up of 3 years 30 patients (25.9%) had died, 20 of them (17.2%) from cardiovascular causes. Average mean transvalvular gradients remained stable up to 5-year follow up (P=0.92), but clinically relevant SVD occurred in 3/99 patients (3.0%), and 15/99 patients (15.1%) had subclinical SVD. One patient with SVD had redo ViV-TAVR.	Lager studies included in table 2.
Descoutures F, Himbert D, Radu C, et al. Transarterial Medtronic CoreValve system implantation for degenerated surgically implanted aortic prostheses. Circ Cardiovasc Interv 2011;4:488–94.	Case series n=10 VIV-TAVI median follow up of 5 months	Procedural success rate was 100%. There was 1 in-hospital death, 1 stroke with moderate sequelae, and 1 pacemaker implantation. The mean post-implantation transprosthetic gradient was 13_7 mmHg; periprosthetic regurgitation was absent or trivial in 9 cases and grade 2 in 1. survivors were in NYHA classes I or II.	Larger studies with longer follow up in table 2.
Dvir D, Assali A, Vaknin-Assa H et al. (2011). Transcatheter aortic and mitral valve implantations for failed bioprosthetic heart valves. Journal of	Case series n=6 Follow up: 30 days	Procedural success and 30 days survival rates 100% Functional class improved (p<0.001).	ViV in aortic (4) and mitral (2) position. Results not reported separately.

Invasive Cardiology 23: 377–81.	Failed bioprosthetic valves (regurgitation, stenotic). Device: ViV CoreValve, Edwards Sapien.		Larger studies included in table 2.
Dvir D, Barbanti M, Tan J, and Webb JG (2014). Transcatheter Aortic Valve-in-Valve Implantation for Patients With Degenerative Surgical Bioprosthetic Valves. Current Problems in Cardiology.39 (1) (pp 7-27), 2014.Date of Publication: January 2014. (1) 7–27.	Review	Implantation of a transcatheter valve inside a failed surgical valve (valve-in-valve procedure) is an alternative, less-invasive option. Although the procedure is similar in some aspects to TAVI in the setting of native aortic valve stenosis, there are many differences that deserve special consideration. We review the potential and challenges of valve-in-valve implantation in patients with failing surgical aortic bioprostheses.	Review
Dvir D, Webb JG (2015). Transcatheter Aortic Valve-in-Valve Implantation for Patients With Degenerative Surgical Bioprosthetic Valves. Circulation Journal; 79: 695–703.	Review	ViV-TAVI inside failed surgically implanted bioprostheses (valve-in-valve) is a new less-invasive alternative to repeat surgery. We review the potential and challenges of valve-in-valve implantation in patients with failing surgical aortic bioprostheses.	Review
Dvir D, Webb J, Brecker S et al (2012). Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves: Results From the Global Valve-in-Valve Register. Circulation. 126:2335–44.	Case series (global VIV register) n=202 degenerated bioprosthetic valves Follow up: mean 289 days	Procedural success was achieved in 93.1% of cases. Adverse procedural outcomes included initial device malposition in 15.3% of cases and ostial coronary obstruction in 3.5%. After the procedure, valve maximum/mean gradients were 28.4_14.1/15.9_8.6 mmHg, and 95% of patients had<1 degree of aortic regurgitation. At 30-day follow up, all-cause mortality was 8.4%, and 84.1% of patients were at New York Heart Association functional class I/II. One-year follow up was obtained in 87 patients, with 85.8% survival of patients who had treatment.	Larger studies with longer follow up included in table 2.
Dvir D., Khan J et al (2018). Novel strategies in aortic valve-in-valve therapy including bioprosthetic valve	Review	There are 2 major adverse events associated with aortic valve-in-valve procedures. Residual stenosis is the ‘Achilles' heel’ of aortic valve-	Review

fracture and BASILICA. Eurointervention (14) AB AB74-AB82.		in-valve, while coronary obstruction is an uncommon but life-threatening adverse event. Bioprosthetic valve ring fracture and bioprosthetic or native aortic scallop intentional laceration may prevent iatrogenic coronary artery obstruction. (BASILICA) may enable some solution.	
Dvir D, Webb JG et al (2017). Transcatheter Aortic Valve Replacement for Failed Surgical Bioprostheses: Insights from the PARTNER II Valve-in-Valve Registry on Utilizing Baseline Computed-Tomographic Assessment. Structural Heart (1) 1-2 34-39 04.	PARTNER II valve-in-valve registry N=84 patients with failed surgical aortic bioprostheses who had CT before VIV-TAVI	CT average annulus internal area was 331.64 +/- 73.52mm. Post SAPIEN XT implantation mean gradient was 17.95 +/- 7.59 mmHg and average aortic valve area was 1.06 +/- 0.35 cm. Small internal annular area per CT was significantly associated with increased gradients in intermediate/large surgical valves (true ID>20 mm, p=0.01). ROC curve for the evaluation of predictability of CT measured area on post-procedural gradients in intermediate/large surgical valves was high (AUC 0.81). Cut off of 329 mm had negative predictive value of 95%. CT-derived annulus area in cases with intermediate and large surgical valves can identify cases at risk for poor haemodynamics after valve-in-valve and influence clinical decision making.	Lager studies included in table 2.
Diemert P, Seiffert M et al (2014). Valve-in-valve implantation of a novel and small self-expandable transcatheter heart valve in degenerated small surgical bioprostheses: The Hamburg experience. Catheter.Cardiovasc Interv, 84: 486–93.	Retrospective case series n=16 Patients with degenerated small aortic bioprostheses VIV i with Medtronic CoreValve Follow up: 30 days	Implantation was successful without relevant remaining aortic regurgitation or signs of stenosis and a marked reduction in post-procedural gradients was seen in 14 out of 16 patients. The mean gradient was reduced from 34 mmHg (SEM 10 mmHg) to 14 mmHg (SEM 6 mmHg). No major device- or procedure-related adverse events occurred during 30-day follow up and clinical improvement was observed.	Larger studies with longer follow included in table 2. Included in systematic review added to table 2 (Phan, 2016)
Diemert, P., Lange, P., Greif, M., et al (2014). Edwards Sapien XT valve placement as treatment option for aortic regurgitation after transfemoral CoreValve implantation: a multicenter	n=11 case series 30-day follow up	Successful implantation in all resulting in a reduction of aortic regurgitation to mean grade 0.23 ± 0.39. Two patients needed permanent pacemaker. After 30 days, 10 patients were alive, whereas 1 patient succumbed to pneumonia	Larger studies included in table 2.

experience. Clin.Res.Cardiol, 103, 183–90.		complicating advanced chronic obstructive pulmonary disease.	
Duncan A, Davies S et al (2015). Valve-in-valve transcatheter aortic valve implantation for failing surgical aortic stentless bioprosthetic valves: A single-center experience. J Thorac Cardiovasc Surg; 150:91-8.	Case series N=22 patients with failing homograft (n=17), stented porcine valve (n=3), aortic root bioprosthesis (n=1), or native resuspended aortic valve (n=1) had VIV-TAVI follow up: 1 year	The 30-day mortality was 0%. No cases occurred of myocardial infarction, tamponade, stroke, severe bleeding, acute kidney injury, or major vascular complications. 3 instances of device migration, and 1 of device embolisation, occurred. Permanent pacing was needed in 14%. Paravalvular aortic regurgitation was absent or mild in 19, and mild to moderate in 3. Average hospital stay was 8 days; all patients were discharged home. Six-month and 1-year mortality was 4.8% and 14.3%, respectively. Aortic valve area and paravalvular aortic regurgitation were unchanged at 1 year.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Chen 2016)
Eggebrecht H, Schafer U, Treede H et al. (2011) Valve-in-valve transcatheter aortic valve implantation for degenerated bioprosthetic heart valves. Journal of the American College of Cardiology: Cardiovascular Interventions 4: 1218–27	VIV-TAVI registry (retrospective) 47 patients at high risk with degenerated aortic surgical bioprosthesis. Technique: ViV-TAVI. Follow up: 30 days	Technically successful in all patients, 2 patients had implantation of a second TAVI prosthesis for severe regurgitation during the procedure. There was 1 procedural death as the result of low-output failure. Valvular function was excellent, transvalvular gradients ≥20 mmHg were noted in 44% of patients. Vascular access complications occurred in 6 (13%) patients, and 5 (11%) patients needed pacemaker implantation. Renal failure occurred in 4 (9%) patients. Mortality at 30 days was 17% (1 procedural and 7 post-procedural deaths), with 3 of 8 fatalities the result of non–valve-related septic complications.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Phan, Chen 2016)
Ejiofor JI, Yammine M et al (2016). Reoperative surgical aortic valve replacement versus transcatheter valve-in-valve replacement for degenerated bioprosthetic aortic valves. The Annals of Thoracic Surgery. 102,5: 1452–8.	Retrospective propensity score matched study Patients with degenerated bioprosthetic valves (n=91 [22 TVIV and 69 SAVR) STS risk score matched	Operative mortality was 4.3% (1 of 22) in the SAVR group and 0 for TAVI ViV (p=1.00). Mean postoperative gradient was 13.5 ± 13.2 mmHg for SAVR and 12.4 ± 6.2 mmHg for TViV (p=0.584). There was no coronary obstruction in either group, but 22% of TViV (5 of 22) had mild paravalvular leaks versus none in the SAVR	Larger studies included in table 2. Included in systematic reviews added to table 2 (Tam, Gozdek 2018).

	VIV n=22 versus Redo SAVR n=22 Follow up: 3 years (Kaplan−Meier Survival Curve)	group (p=0.048). Postoperative stroke rate was 9% (2 of 22) for SAVR and 0 for TViV (p=0.488). The TViV group had shorter median length of stay (5 versus 11 days, p=0.001). Actuarial survival at 3 years was 76.3% (95% confidence interval: 58.1 to 94.5) versus 78.7 (95% confidence interval: 56.2 to 100) for SAVR and TViV, respectively (p=0.410).	
Erlebach M, Wottke M et al (2015). Redo aortic valve surgery versus transcatheter valve-in-valve implantation for failing surgical bioprosthetic valves: consecutive patients in a single-center setting. J Thorac Dis; 7(9):1494–500	Retrospective comparative case series N=102 patients with failed surgical bioprosthetic valves VIV-TAVI n=50 versus Redo SAVR n=52 Follow up: 1 year (Kaplan−Meier Survival Curve)	Patients in the TAV-in-SAV group had a lower mean left ventricular ejection fraction than patients in the SAV-in-SAV group (49.8±13.1 versus 56.7±15.8, P=0.019). Postoperative pacemaker implantation and chest tube output were higher in the SAV-in-SAV group compared to the TAV-in-SAV group [11 (21%) versus 3 (6%), P=0.042 and 0.9±1.0 versus 0.6±0.9, P=0.047, respectively]. There was no statistically significant difference in myocardial infarction, stroke or dialysis postoperatively. Thirty-day mortality was not significantly different between the 2 groups [TAV-in-SAV2 (4%) versus SAV-in-SAV0, P=0.238]. Kaplan−Meier 1-year survival was statistically significantly lower in the TAV-in-SAV group than in the SAV-in-SAV group (83% versus 96%, P<0.001).	Larger studies included in table 2. Included in systematic reviews added to table 2 (Tam, Gozdek 2018).
Faerber, G., Schleger, S et al (2014). Valve-in-Valve Transcatheter Aortic Valve Implantation: The New Playground for Prosthesis-Patient Mismatch. J Interv Cardiol.	Review	PPM may impact significantly on haemodynamic outcome after VIV-TAVI. 15% of published VIV procedures show only a minimal reduction of pressure gradients. We will address potential pitfalls in the current determination of PPM, outline the missing links for reliable determination of PPM, and present a simplified algorithm to guide decision making for VIV-TAVI.	Review
Ferrari E (2012). Transcatheter aortic “valve-in-valve” for degenerated bioprostheses: Choosing the right TAVI valve. Ann	Review	Valve-in-valve procedures represent a less-invasive approach in patients at high risk and the published results are very encouraging. Technical success rates of 100% have been reported, as	Review

Cardiothorac Surg;1(2):260–2		have the absence of paravalvular leaks, acceptable transvalvular gradients and low complication rates. The current article focuses on choosing the correct transcutaneous valve to match the patient's existing bioprosthesis for valve-in-valve procedures.	
Ferrari E, Stortecky S et al (2019). The hospital results and 1-year outcomes of transcatheter aortic valve-in-valve procedures and transcatheter aortic valve implantations in the native valves: the results from the Swiss-TAVI Registry. European Journal of Cardiothoracic Surgery (27) 27.	Swiss-TAVI Registry N=157 VIV-TAVI in degenerated bioprostheses versus 4599 TAVI in native valve (retrospective comparative analysis) Follow up: 1 year	VinV patients showed higher predischarge transvalvular mean gradients (14.14 +/- 7.9 mmHg vs 8.42 +/- 5.0 mmHg; P<0.001), smaller mean valve surface area (1.54 +/- 0.7 cm2 vs 1.83 +/- 0.5 cm2; P<0.001) and a lower risk of moderate/severe paravalvular leak (1.3% vs 5%). Post-procedural kidney injury (1.3% vs 4.8%; P=0.06) and new pacemakers (3.3% vs 18.5%; P<0.001) were higher after TAVI. All-cause mortality and cardiovascular mortality at 30 days were similar between the 2 groups (1.9% vs 3.8%; P=0.242 and 1.9% vs 3.4%; P=0.321), whereas after 1-year, all-cause mortality was lower for VinV patients (6.8% vs 13%; P=0.035). VinV aortic procedures showed favourable 30-day and 1-year clinical outcomes compared with TAVI procedures for the native aortic valve disease.	Lager studies included in table 2.
Ferrari E, Marcucci C, Suzler C et al. (2010). Which available transapical transcatheter valve fits into degenerated aortic bioprostheses? Interactive Cardiovascular and Thoracic Surgery 11: 83–5.	Case series n=6 Device: Edwards Sapien Patients with degenerated bioprosthesis.	Success rate: 100% Mean transvalvular gradient 18 mmHg. No leaks. 30-day mortality: 0%	Larger studies included in table 2.
Frerker C, Schewel J et al (2015). Expansion of the Indication of Transcatheter Aortic Valve Implantation — Feasibility and Outcome in "Off-Label" Patients Compared With "On-Label" Patients. Journal of Invasive Cardiology. 27, 5, 29–236.	Retrospective case series N=591 patients who had TAVI Group A (on label)-n=435 Group B (off label - 156 patients, VIV n=30)	Overall device success was 90% (91.3% in group A versus 86.5% in group B; P=.02). Overall 30-day mortality was 9.7%. Group B had a higher 30-day mortality compared with group A (14.7% versus 7.8%, respectively; P=.01). Group B.5 had the lowest 30-day mortality (3.3%) Subgroup analysis	Larger studies included in table 2.

		12-month survival rate was higher in patients with ViV (off-label group B.5; 76.7%) compared with group A (79.5%; P=.82). the rate of new pacemakers in patients who had ViV was 0% compared with 23% in group A (*P*=.01).	
Gaia DF, Couto A, Breda JR et al (2012). Transcatheter aortic valve-in-valve implantation: A selection change? OT - Implante valve-in-valve transcateter em posicao aortica: Uma mudanca de selecao? Brazilian Journal of Cardiovascular Surgery.27 (3) (pp 355–61), 2012.	Retrospective case series n=14 Patients with double aortic bioprosthesis dysfunction follow up: 1-30 months	Correct prosthetic deployment in 100% cases. There was no conversion. There was no operative mortality. 30-day mortality was 14.3% (2/14). LVEF increased significantly 51 to 55.6 ($p<0.01$) after the 7th postoperative day. Aortic gradient significantly reduced. Residual aortic regurgitation was not present. There were no vascular complications or complete atrioventricular block.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Phan, Chen 2016).
Gandolfo C, Turrisi M et al (2018). Acute Obstructive Thrombosis of Sapien 3 Valve After Valve-in-Valve Transcatheter Aortic Valve Replacement for Degenerated Mosaic 21 Valve. Jacc: Cardiovascular Interventions (11) 2 215-217.	Case report VIV-TAVI	This case of hyperacute life-threatening obstructive ViV thrombosis seems significant enough to warrant a careful follow up especially after ViV procedures of certain types of failed surgical valve.	Larger studies included in table 2
Gasior T, Huczek Z et al (2017). Aortic valve-in-valve procedures for treatment of failing surgically implanted bioprosthesis. COR ET VASA 59, e35–e41.	Review	Current clinical experience with VIV includes balloon-expandable and self-expandable valves. Long-term outcomes in real life registries are favourable. Key problems are high residual gradient, coronary obstruction and paravalvular leak. Use of new-generation devices will likely improve the outcomes of VIV.	Review
Goleski PJ, Reisman M and Don CW (2018). Reversible thrombotic aortic valve restenosis after valve-in-valve transcatheter aortic valve replacement. Catheterization & Cardiovascular Interventions (91) 1 165-168.	Case report N=3 VIV-TAVI	We present 3 cases of valve-in-valve (VIV) restenosis following TAVR with the balloon-expandable transcatheter heart valves, presumably because of valve thrombosis that improved with anticoagulation.	Larger studies included in table 2.
Gonska B, Seeger J et al (2016). Transfemoral valve-in-valve implantation	Case series N=9 patients (7 AR, 2 AS of surgical aortic	Successful implantation was reported in all patients, the mean echographic gradients	Larger studies included in table 2.

for degenerated bioprosthetic aortic valves using the new balloon-expandable Edwards Sapien 3 Valve. Catheterization and Cardiovascular Interventions 88: 636–43.	bioprosthesis) had VIV-TAVI (Edwards Sapien 3 valve). Follow up: 30 days.	decreased from 42mmHg to 18mmHg (p<0.01). Device success (VARC 2 criteria) was achieved in 8/9 patients. There was no death, coronary obstruction, access site complications, bleeding, vascular injury, use of second valve or need for post-dilation. 2 patients needed pacemaker implantation within 7 days, no AR was seen. Early safety event occurred in 1 patient.	
Gotzmann M, Mugge A and Bojara W (2010). Transcatheter aortic valve implantation for treatment of patients with degenerated aortic bioprosthesis valve-in-valve technique. Catheterization and Cardiovascular Interventions 76: 1000–06.	Case series n=5 single centre Follow up=72 days (mean) patients with degenerated aortic bioprosthesis Transfemoral-TAVI 26 mm CoreValve (Medtronic) BAV before implantation.	Procedural success 100%; immediate decrease of transaortic peak-to-peak pressure (p=0.002). Mean gradient-16.4 ± 3.6. NHYA functional class improved in all patients. Left ventricular ejection fraction increased (p=0.019). Mild AR-2 patients. New permanent pacemaker-1 patient (left bundle branch block and AVB). Major adverse cardiac and cerebrovascular events did not arise.	Larger studies included in table 2.
Gozdek M, Raffa GM et al (2018). Comparative performance of transcatheter aortic valve-in-valve implantation versus conventional surgical redo aortic valve replacement in patients with degenerated aortic valve bioprostheses: systematic review and meta-analysis. European Journal of Cardiothoracic Surgery. 53, 495-504.	systematic review and meta-analysis of redo sAVR with ViV-TAVI for patients with failed degenerated aortic bioprostheses 5 observational studies included (n=342)	There was no statistical difference in procedural mortality (RR 0.74, 95% CI 0.18–2.97; P = 0.67], 30-day mortality (RR 1.29, 95% CI 0.44–3.78; P = 0.64) and cardiovascular mortality (RR 0.91, 95% CI 0.30–2.70; P = 0.86) at a mean follow-up period of 18 months, cumulative survival analysis favoured surgery with borderline statistical significance (ViV-TAVI versus re-sAVR: hazard ratio 1.91, 95% CI 1.03–3.57; P = 0.039). ViV-TAVI was associated with a significantly lower rate of permanent pacemaker implantations (RR 0.37, 95% CI 0.20–0.68; P = 0.002) and shorter intensive care unit (P < 0.001) and hospital stays (P = 0.020). Redo-SAVR offered superior echocardiographic outcomes: lower incidence of patient–prosthesis mismatch (P = 0.008), fewer paravalvular leaks (P = 0.023) and lower mean postoperative aortic	Comprehensive meta-analysis of similar comparison with latest studies included in table 2.

		valve gradients in the prespecified analysis (P = 0.017). The ViV-TAVI approach is a safe and feasible alternative to re-sAVR that may offer an effective, less-invasive treatment for those who are inoperable or at high risk. Re-sAVR should remain the standard of care, particularly in the low-risk population, because it offers superior haemodynamic outcomes with low mortality rates.	
Gozdek M, Raffa GM, et al (2017). Kubica J, et al. Comparative performance of transcatheter aortic valve-in-valve implantation versus conventional surgical redo aortic valve replacement in patients with degenerated aortic valve bioprostheses: systematic review and meta-analysis. Eur J Cardiothorac Surgery.	Systematic review and meta-analysis comparing ViV-TAVI with re-sAVR in patients with failing degenerated aortic bioprostheses 5 studies (n=342)	Although there was no statistical difference in procedural mortality (RR 0.74, 95% CI 0.18–2.97; P = 0.67], 30-day mortality (RR 1.29, 95% CI 0.44–3.78; P = 0.64) and cardiovascular mortality (RR 0.91, 95% CI 0.30–2.70; P = 0.86) at a mean follow-up period of 18 months, cumulative survival analysis favoured surgery with borderline statistical significance (ViV-TAVI versus re-sAVR: hazard ratio 1.91, 95% CI 1.03–3.57; P = 0.039). ViV-TAVI was associated with a significantly lower rate of permanent pacemaker implantations (RR 0.37, 95% CI 0.20–0.68; P = 0.002) and shorter intensive care unit (P < 0.001) and hospital stays (P = 0.020). In contrast, re-sAVR offered superior echocardiographic outcomes: lower incidence of patient–prosthesis mismatch (P = 0.008), fewer paravalvular leaks (P = 0.023) and lower mean postoperative aortic valve gradients in the prespecified analysis (P = 0.017).	Comprehensive meta-analysis of similar comparison with latest studies included in table 2.
Grubitzsch H, Zobel S et al (2017). Redo procedures for degenerated stentless aortic xenografts and the role of valve-in-valve transcatheter techniques. European Journal of Cardiothoracic Surgery 51, 653–9.	Retrospective comparative case series N=52 patients with failed stentless aortic valves. VIV-TAVI n=27 versus Redo SAVR n=25	Implantation was successful in all surgical and in 24 transcatheter cases. Procedural complications were aortic dissection (n=1) during reoperation and coronary obstruction (n=4), device malpositioning (n=3), deployment of>1 valve (n=2) and vascular access site complications (n=2) during	Larger studies included in table 2. Included in systematic reviews added to table 2 (Tam, Gozdek 2018).

	Follow up: 1.75 years.	ViV-TAVI. 30-day mortality (10%, 3 ViV-TAVI patients, 2 surgical patients, P=1.0) was associated with preoperative renal failure,>1 concomitant procedure, life-threatening bleeding, coronary obstruction and necessity for prolonged circulatory support. Functional (94% NYHA Class I/II) and echocardiographic results (indexed effective orifice area 0.95 ± 0.27 cm2/m2, mean transvalvular gradient 14 ± 6.8 mmHg) were favourable. Aortic regurgitation was mild and moderate in 2 and 3 patients. 1-year survival was 82.3 ± 5.4% and similar after surgery (83.1 ± 7.7%) and ViV-TAVI (81.5 ± 7.5%, P=0.76).	
Hamid NB, Khalique OK et al (2015). Transcatheter valve implantation in failed surgically inserted bioprosthesis. Review and practical guide to echocardiographic imaging in valve-in-valve procedures. JACC: cardiovascular imaging 8, 8:960–79.	Review	There is an increase need for multimodality imaging for VIV procedures. In this review, the echocardiographic requirements for optimal patient selection, procedural guidance, and immediate post-procedural assessment for VIV procedures are summarised.	Review
Huber C, Praz F et al (2015). Transcarotid aortic valve-in-valve implantation for degenerated stentless aortic root conduits with severe regurgitation: a case series. Interactive CardioVascular and Thoracic Surgery 20, 694–700	Case series N=3 patients with complex vascular anatomy had VIV-TAVI via transcarotid route (CoreValve) Follow up: 6 months	All patients had successful procedures, and experienced improvement of symptoms. Mean transvalvular gradient was 3.6 and 11 mmHg. Effective orifice area ranged between 1.7 and 2.2cm2.	Larger studies included in table 2.
Huczek Z, Grodecki K (2018). Transcatheter aortic valve-in-valve implantation in failed stentless bioprostheses. Journal of Interventional Cardiology (31) 6 861-869.	Case series POL-TAVI registry N=45 ViV-TAVI in degenerated stentless bioprostheses (25 failed stented valves versus 20 stentless valves) and propensity matched with 45 degenerated native aortic valves). mean follow up: 633 days	Using VARC-2 composite endpoints, ViV-TAVI in stentless prostheses was characterized by a lower device success (50% vs 76% in stented vs 88.9% in native TAVI, P<0.001), but comparable early safety up to 30 days (73.7% vs 84% vs 81.8%, respectively, log-rank P=0.667) and long-term clinical efficacy beyond 30 days (72.2% vs 72% vs 73.8%, respectively, log-rank P=0.963). Despite technical challenges and a lower device success, ViV-TAVI in stentless	Lager studies included in table 2.

		aortic bioprostheses achieves similar safety, efficacy, and functional improvement as in stented or degenerated native valves.	
Ihlberg L, Nissen H, Nielsen NE et al (2013). Early clinical outcome of aortic transcatheter valve-in-valve implantation in the Nordic countries. Journal of Thoracic & Cardiovascular Surgery 146 (5) 1047–54.	Nordic VIV Registry (retrospective data) 45 ViV-TAVI Follow up: mean 14.4 months	No intraprocedural mortality. Technical success rate was 95.6%.The all-cause 30-day mortality was 4.4% (1 cardiac-related and 1 aspiration pneumonia). The major complications within 30 days included stroke in 2.2%, periprocedural myocardial infarction in 4.4%, and major vascular complication in 2.2% of patients. At 1 month, all but 1 patient had either no or mild paravalvular leakage. The 1-year survival was 88.1%.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Phan, Chen 2016).
Jose J, Sulimov DS et al (2017). Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement. JACC Cardiovascular Interventions, 10 (7), 686–97.	Retrospective analysis N=642 patients who had TAVI.	The overall incidence of clinical valve thrombosis was 2.8% (n=18) characterized by imaging abnormalities and increased gradients and N-terminal pro–brain natriuretic peptide levels. Thrombosis occurred significantly more often with balloon-expandable valves (odds ratio: 3.45; 95% confidence interval: 1.22 to 9.81; p=0.01) and following valve-in-valve procedures (n=43; odds ratio: 5.93; 95% confidence interval: 2.01 to 17.51; p=0.005). Median time to diagnosis of valve thrombosis was 181 days.	Larger studies included in table 2.
Jubran A, Flugelman MY et al (2019). Intraprocedural valve-in-valve deployment for treatment of aortic regurgitation following transcatheter aortic valve replacement: An individualized approach. International Journal of Cardiology (02) 02.	TAVR registry VIV-TAVI N=285	In group-1 (supra-annular cases, n=6), second valves were implanted 9+/-4mm lower than the initial valves. In group-2 (intra annular cases, n=3), second valves were implanted 7+/-4mm higher than the initial valves. In group-3 (infra annular cases, n=2), second valves were implanted 9+/-1mm higher than the initial valves. Valve-in-valve deployment reduced AR grade in all 3 groups.	Lager studies included in table 2.
Hamudi J, Jaffe R et al (2018).Transoesophageal echocardiography guided emergency valve-in-valve transcatheter aortic valve implantation. European	Case report N=1		Larger studies included in table 2.

heart journal cardiovascular Imaging (19) 6 713 06 01.			
Khan A and Dangas, G (2018).Transcatheter valve-in-valve for failing bioprosthetic aortic valve: Usually a good idea. Catheterization & Cardiovascular Interventions (92) 7 1412-1413.	Review	Surgical redo aortic valve replacements for failed surgical aortic bioprostheses have been traditionally considered the standard practice; however, in patients with higher surgical risk scores, transcatheter valve-in-valve aortic valve replacements are being commonly performed There is scarcity of data comparing these 2 approaches in this complex patient cohort Available data suggest that transcatheter ViV aortic valve replacement is generally a safe approach once some caveats are accounted for.	Review
Kempfert J, Van Linden A et al (2010). Transapical off-pump valve-in-valve implantation in patients with degenerated aortic xenografts. Annals of Thoracic Surgery, 89:1934–41.	Case series Prospective N=11 patients with degenerated xenografts had ViV-TAVI using the Edwards Sapien THV (treated off pump). Follow up 330 ± 293 days (range, 15 to 1,007),	Implantation was successful in all, Post implantation there was no paravalvular incompetence in any and mild (first degree) central incompetence in 2 patients. Sufficient flaring of the inflow and outflow parts of the Sapien prosthesis was observed in all patients, suggesting a stable position and an almost absent risk of late embolisation. Maximal transvalvular pressure gradients were 21 ± 8 mmHg, and mean echocardiographic pressure gradients were 11 ± 4 mmHg. All patients were well and alive at follow up.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Phan, Chen 2016).
Khawaja MZ, Haworth P, Ghuran A et al. (2010) Transcatheter aortic valve implantation for stenosed and regurgitant aortic valve bioprosthesis CoreValve for failed bioprosthetic aortic valve replacements. Journal of the American College of Cardiology 55: 97–101	Case series n=4 Follow up: 2–6 months Patients with stenotic and regurgitant degenerative surgical aortic valve bioprosthesis. Implant size: 26 mm CoreValve (Medtronic)	Immediate results show good haemodynamic status with low transvalvular gradient and no AR. Improvement in NHYA functional class from III or IV to I or II. 30-day survival: 100% 1 patient with a left subclavian approach developed a pale, cold and pulseless arm after the procedure because of occlusive subclavian artery dissection. A 7 x 80 mm life stent flexstar was implanted, balloon aortic valvuloplasty was done and this decreased the transaortic gradient.	Larger studies with longer follow up included in table 2.

Koizumi S, Ehara N et al (2018). A case of SAPIEN XT valve fallen into left ventricle during valve-in-valve transcatheter aortic valve implantation. General Thoracic & Cardiovascular Surgery (66) 5 291-293.	Case report N=1 VIV-TAVI using transfemoral approach done in a patient with TAVI valve migration to LVOT 41 days after implantation	As soon as the second transcatheter heart valve touched the first implanted valve, it fell into the left ventricle. Immediate surgical intervention was required. The first valve was removed, and surgical aortic valve replacement was successfully performed. In conclusion, we should choose surgical aortic valve replacement for late transcatheter heart valve embolisation.	Larger studies included in table 2.
Latib A, Ielasi A et al (2012). Transcatheter valve-in-valve implantation with the Edwards SAPIEN in patients with bioprosthetic heart valve failure: the Milan experience. EuroIntervention, 7: 1275–84.	Retrospective case series N=18 patients at high risk with symptomatic bioprosthetic failure had ViV- TAVI (TF approach). Follow up: 1 year.	Device success was achieved in all but 1 patient who had a final transaortic gradient ≥20mmHg. Acute kidney injury occurred in 3 patients, life-threatening or major bleeding in 4 patients, major vascular complications occurred in 1 patient, permanent pacemaker implantation in 2 patients. There were no deaths or neurological events at 30-day follow up. At a median follow up of 11 months mortality rate was 5.6% and all patients were in NYHA class II or lower.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Phan, Chen 2016).
Landes U, Dvir D et al (2019). Transcatheter Aortic Valve-in-Valve Implantation in Degenerative Rapid Deployment Surgical Bioprosthesis. Eurointervention (19) 19	Comparative case series (VIVD international registry) Propensity score matched analysis N=30 ViVr rapid deployment versus 2288 conventional ViVc	Implantation was successful in all ViVr cases and, compared with ViVc, associated with equally favourable hemodynamic outcomes [mean gradient (mmHg): 14.6 +/- 8.3 vs. 16.2 +/- 8.9, p=0.356; regurgitation>=mild: 3.7% vs. 5.2%, p=0.793]. Periprocedural complications rates were similar and low in both groups. There was no coronary obstruction event in any ViVr case, and 1 (3.6%) patient died during 1-year follow up. ViVr appears effective, safe and associated with favourable hemodynamic outcome.	Lager studies included in table 2.
Kofler M, Unbehaun A et al (2019). Transcatheter Valve-in-Valve and Valve-in-Ring Interventions for Failing Bioprostheses and Annuloplasty Rings. Surgical Technology International (34) 18.	Review	This review focuses on individualized patient selection, procedure-specific risk factors and technical aspects of transcatheter ViV/R interventions and explores the currently available literature on postinterventional outcome.	Review
Linke A, Woitek F et al (2012). Valve-in-valve implantation of Medtronic	Retrospective case series	In 25 patients the mean gradient declined from 42±16 mmHg before to 18±8 mmHg	Larger studies included in table 2. Included in

CoreValve prosthesis in patients with failing bioprosthetic aortic valves. Circ Cardiovascular Interventions, 5:689–97.	N=27 patients with failed bioprosthetic aortic valves treated with ViV-TAVI	after MCV implantation (P<0.001), the level of AR declined by 2. There was no intraprocedural death and myocardial infarction. The rate of major stroke was 7.4 %, of life-threatening bleeding 7.4%, of kidney failure stage III 7.4%, and major access site complication 11.1 %, respectively. Within 30 days after the procedure, 2 patients died; 1 from stroke and 1 from cardiac failure (30-day mortality: 7.4%).	systematic reviews added to table 2 (Phan, Chen 2016).
Long, A. and Mahoney, P (2018). Fulminant presentation of a failed TAVR valve: Successful revision with a transcatheter approach - Case report and review of the literature. Cardiovascular Revascularization Medicine (18) 18.	Case report	We report here a successful case of emergent, catheter-based treatment for severe, highly symptomatic valve-in-valve restenosis of a 5-year-old Sapien valve.	Larger studies included in table 2.
Loyalka P, Nascimbene A et al (2017). Transcatheter aortic valve implantation with a Sapien 3 Commander 20mm valves in patients with degenerated 19mm bioprosthetic aortic valve. Catherization Cardiovascular Interventions, 89 (7), 1280-85.	N=5 patients with AS had VIV-TAVI (Edwards Sapien 3 valves) into degenerated bioprosthetic valves.	Post deployment assessment confirmed absence of mild aortic insufficiency and no increase in transaortic gradient when compared to naive 19mm bioprosthetic valve.	Larger studies included in table 2.
Lopez S, Meyer P et al (2018). Transcatheter valve-in-valve implantation in a degenerated very small Mitroflow prosthesis. Interactive CardioVascular and Thoracic Surgery 1–6.	Case series N=18 VIV-TAVI procedures in patients with degenerated 19mm and 21mm Mitroflow bioprostheses. Follow up: 6 months	Procedure was successful in 94% (17/18) patients. For implantations above the limit of −6 mm, the mean gradient was 10.4 ± 2.6 mmHg compared with 28.1 ± 11.6 mmHg for implantations below the limit of −6 mm (P < 0.01). For patients with severe stenosis, the mean post-procedural gradient was 31.2 ± 11.8 mmHg compared with 12.7 ± 6 mmHg in the absence of severe stenosis (P < 0.01). Patient–prosthesis mismatch (indexed effective orifice area ≤ 0.85 cm2/m2) and severe mismatch (indexed effective orifice area ≤ 0.65 cm2/m2) were present in 83% (15 of 18) and 27% (5 of 18) of patients, respectively.	Larger studies included in table 2.

		Functional status was improved in all patients.	
Mangner N, Holzhey D et al (2018). Treatment of a degenerated sutureless Sorin Perceval valve using an Edwards SAPIEN 3. Interactive Cardiovascular & Thoracic Surgery (26) 2 364-366.	Case report	In a 75-year-old patient with a degenerated Perceval valve with severe valvular aortic regurgitation and stenosis an Edwards SAPIEN 3 was implanted leading to an immediate haemodynamic improvement. A cerebral protection device caught a big embolised piece of material in the left carotid artery filter. The case shows that not only suture-based stented and stentless bioprostheses can be treated by a valve-in-valve strategy, but it is also feasible to treat a failed sutureless Sorin Perceval using a balloon-expandable SAPIEN 3.	Lager studies included in table 2.
Meneguz-Moreno RA, Siqueira DA et al (2015). Transcatheter valve-in-valve implantation for surgical aortic bioprosthesis dysfunction. Rev Bras Cardiol Invasiva;23(3):166–72.	Case series N=7 patients with surgical bioprosthesis dysfunction had aortic VIV implantation	Procedural success was achieved in 85.7% (6/7) cases. The mean gradient decreased from 38.2 ± 9.6 mmHg to 20.9 ± 5.9 mmHg, and the valve area increased from 1.2 ± 0.4 cm2 to 1.5 ± 0.5 cm2. After 1 year, there were no deaths and no other statistically significant adverse outcomes; 80% of patients were in NYHA functional class I/II. The transvalvular gradients and valve area remained unchanged.	Larger studies included in table 2.
Milburn K, Bapat V, and Thomas M (2014). Valve-in-valve implantations: is this the new standard for degenerated bioprostheses? Review of the literature. Clin.Res.Cardiology, 103 (6), 417-429.	ViV-TAVI Patients with degenerated bioprosthesis who are deemed to be a high surgical risk.	This technique can be applied to dysfunctional aortic bioprosthetic valves and can also be used in the pulmonary and atrioventricular valve bioprosthesis. We review the current literature to assess whether this technique may be the new standard for degenerated bioprosthesis.	General review
Moquera VX, Gonzalez-Barbeito M et al (2018). Efficacy and safety of transcatheter valve-in-valve replacement for Mitroflow bioprosthetic valve dysfunction. Journal of Cardiac Surgery, 33: 356–62.	Case series N=11 patients with structural valve deterioration of Mitroflow bioprostheses treated with ViV-TAVI Follow up: 3 years	One patient had a coronary occlusion during the procedure. There was one hospital death. At 1-year follow up, peak and mean aortic gradients were 25.5mmHg and 15.5mmHg. One patient had mild paravalvular regurgitation. Cumulative survival was 90.9% at 1year, 70.7% at 2 years and 53% at 3 years.	Larger studies included in table 2.

Mylotte D, Lange R, Martucci G, Piazza N. Transcatheter heart valve implantation for failing surgical bioprostheses: technical considerations and evidence for valve-in-valve procedures. Heart 2013;99:960-7.		TAV-in-SAV procedures have the potential to become the standard of care for structural valve dysfunction, though large prospective comparisons with long-term follow up are fundamental to the development of the field.	Review
Nalluri N, Atti V et al (2018). Valve in valve transcatheter aortic valve implantation (ViV-TAVI) versus redo-surgical aortic valve replacement (redo-SAVR0: A systematic review and meta-analysis. Journal of Interventional Cardiology. 31: 661–71.	Systematic review and meta-analysis of VIV-TAVI versus redo SAVR for aortic bioprosthetic valve dysfunction. 6 observational studies included (255 ViV-TAVI versus 339 redo SAVR).	There was no statistically significant difference between VIV-TAVI and redo SAVR for procedural, 30 day and 1-year mortality rates. ViV-TAVI was associated with lower risk for PPM (OR 0.43, CI 0.21-0.89; p=0.02) and a trend towards increased risk of paravalvular leak OR 5.45, CI 0.94-31.58; p=0.06. There was no statistically significant difference for stroke, major bleeding, vascular complication ns and post-procedural aortic valvular gradients more than 20mmHg.	Comprehensive review with similar comparison included in table 2.
Napodano M, Gasparetto V, Tarantini G et al. (2011). Performance of valve-in-valve for severe paraprosthetic leaks due to inadequate transcatheter aortic valve implantation. Catheterization & Cardiovascular Interventions 78: 996–1003.	Case series n=6 Follow up: 6–24 months Patients who had valve-in-valve implantation for moderate-to-severe paraprosthetic leaks after TAVI because of prosthesis malposition (too deep implantation). Device: CoreValve (Medtronic) Single centre prospective register of TAVI (Italy).	Device success: 100% Para prosthetic leaks absent (n=2), decreased from severe to mild or trivial (n=4). Pacemaker implants- (n=4). No deaths at 30 days. Deaths: 2 (not related to prosthesis). One was because of heart failure related to chronic anaemia/atrial fibrillation at 2 months and death occurred because of pneumonia complications at day 729. One was caused by GI bleeding, the patient had blood transfusion on the 34th day and died on day 122 because of pulmonary surgery complications. One patient had heart failure at 3-month follow up and was at NYHA class I at 1-year follow up. Valvular pressure gradient, effective orifice area and AR did not change throughout the follow up.	Larger studies included in table 2.

Nelson BC, Chadderdon, S et al (2019). Bioprosthetic aortic valve leaflet disruption with high energy electrocautery to prevent coronary artery obstruction during valve-in-valve transcatheter aortic valve replacement. Catheterization & Cardiovascular Interventions (93) 1 164-168.	Case report	This case describes a successful VIV-TAVR using a simplified concept of the BASILICA technique in a patient where the full procedure could not be completed.	Larger studies included in table 2.
Nerla R, Cremonesi A and Castriota F (2018). Successful percutaneous paravalvular leak closure followed by transfemoral aortic lotus valve-in-valve implantation in a degenerated surgical bioprosthesis. Catheterization & Cardiovascular Interventions (91) 1 169-174.	Case report N=1 case of 65-year-old man with surgical degenerated bioprosthesis had VIV-TAVI replacement (23mm valve). Follow up: 6 months	Normal aortic valve function restored completely, and a dramatic improvement of functional status seen at 6-month follow up. absence of any aortic regurgitation noted.	Larger studies included in table 2.
Neupane S, Singh H et al (2018). Meta-Analysis of transcatheter valve-in-valve implantation versus redo aortic valve surgery for bioprosthetic aortic valve dysfunction. American Journal of Cardiol 121, 1593–600.	Meta-analysis of nonrandomized studies comparing ViV-TAVI versus redo SAVR for aortic bioprosthetic valve dysfunction. N=4 studies (489 patients: 227 ViV-TAVI and 262 redo SAVR)	30-day mortality was similar in 2 groups (5% versus 4%; odds ratio [OR] = 1.08, 95% confidence interval [CI] = 0.44 to 2.62) despite the higher operative risk in the ViV-TAVI cohort as evidenced by significantly higher EuroSCORE I or II. There were similar rates of stroke (2% versus 2%; OR = 1.00, 95% CI = 0.28 to 3.59), myocardial infarction (2% versus 1%; OR = 1.08, 95% CI = 0.27 to 4.33), and acute kidney injury needing dialysis (7% versus 10%; OR = 0.80, 95% CI = 0.36 to 0.1.77) between 2 groups but a lower rate of permanent pacemaker implantation in the ViV-TAVI group (9% versus 15%; OR = 0.44, 95% CI = 0.24 to 0.81). This meta-analysis of nonrandomized studies with modest number of patients suggested that ViV-TAVI had similar 30-day survival compared with redo-SAVR for aortic BPV dysfunction.	Comprehensive meta-analysis of similar comparison with latest studies included in table 2.

Ochiai T, Yoon SH et al (2018). Outcomes of self-expanding versus balloon-expandable transcatheter heart valves for the treatment of degenerated aortic surgical bioprostheses. Circulation Journal 82:2655–62.	Propensity score matched study (37 pairs) N=135 patients with degenerated aortic surgical valves having ViV-TAVI with early or new-generation valves Supra-annular self-expanding THV=40 versus balloon-expandable THV n=95. Median follow up=202 days	Post-procedural mean gradient was significantly lower in the self-expanding THV group than in the balloon-expandable THV group (12.1±6.1 mmHg versus 19.0±7.3 mmHg, P<0.001). The incidence of at least mild post-procedural aortic regurgitation (AR) was comparable between the self-expanding and balloon-expandable THV groups (21.6% versus 10.8%, P=0.39). In the self-expanding THV group, the new-generation THV showed a trend towards a lower incidence of at least mild AR compared with the early-generation THV (12.5% versus 38.5%, P=0.07). A similar trend was observed in the balloon-expandable THV group (4.2% versus 23.1%, P=0.08). There was no statistically significant difference between the self-expanding and balloon-expandable THV groups in the cumulative 2-year all-cause mortality rates (22.4% versus 43.4%, log-rank P=0.26).	Comparison between self-expandable and balloon-expandable valves.
Onofrio AD, Tarja E et al (2016). Early and midterm clinical and hemodynamic outcomes of transcatheter valve in valve implantation: results from a multicenter experience. Annals of Thoracic Surgery, 102: 1966-73.	Retrospective case series N=65 patients who had VIV VIV –Aortic (n=44) VIV-mitral (n=22) VIV aortic +mitral (n=) Mean follow up=14 months	All-cause 30-day mortality was 4.5% and 9% in VIV-A and VIV-M respectively (2 patients in each group). Kaplan−Meier survival in VIV-A patients at 1,2 3 and 4 years was 80%, 75%, 68% and 54% respectively. Survival at 3 years of VIV-M patients was 91%. A statistically significant improvement of NYHA functional class was seen at follow up.	Larger studies included in table 2.
Patel JS, Krishnaswamy A et al (2017). Optimizing hemodynamics of transcatheter aortic valve-in-valve implantation in 19mm surgical aortic prostheses. Catheter Cardiovasc Interv 92; 550–4.	Case series N=5 patients who had VIV-TAVI in 19mm degenerated surgical aortic bioprosthetic valves. Follow up: post implant.	All procedures were successful. In all patients mean aortic valve gradients significantly improved post VIV-TAVI after post-dilation.	Larger studies included in table 2.
Piazza N, Bleiziffer S, Brockmann G, et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical		A comprehensive review of the design and failure modes of SAVs and the procedural steps involved in TAV-in-SAV procedures.	Review

application and evaluation (part 1). JACC Cardiovasc Interv 2011;4:721-32.			
Piazza N, Bleiziffer S, Brockmann G et al. (2011) Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 2). Jacc: Cardiovascular Interventions 4: 733–42.	Case series (prospective) 20 patients at high surgical risk with failed surgical aortic bioprosthesis (stenosis 10, regurgitation 9, both 1) Technique -TAVI in surgical aortic valve (SAV) implantation. Follow up: within 30 days	Successful implantation in 18 of 20 patients. The mean transaortic valve gradient was 20.0 ± 7.5 mmHg. None-to-trivial, mild, and mild-to-moderate paravalvular aortic regurgitation was observed in 10, 6, and 2 patients, respectively. We experienced 1 intraprocedural death following pre-implant balloon aortic valvuloplasty (“stone heart”) and 2 further in-hospital deaths because of myocardial infarction.	Larger studies included in table 2.
Piazza N, Schultz C, De Jaegere PPT et al. (2009). Implantation of 2 self-expanding aortic bioprosthetic valves during the same procedure- Insights into valve-in-valve implantation (“Russian Doll Concept”). Catheterization and Cardiovascular Interventions 73: 530–9.	Case series n=5 Patients with acute failure of TAVI because of malpositioning or valve under sizing. Valve-in-valve implantation of 2 self-expanding aortic bioprostheses during the same procedure. Follow up ranged from post procedure to 1 year.	In 2 cases the first valve was implanted too high and migrated causing severe AR. After second valve implant trivial AR and statistically significant reduction in transvalvular gradients were noted. Procedural complications in 1 case included progressive pericardial effusion, hypotension, left bundle branch block, haemodynamic instability. Surgical exploration revealed cardiac tamponade, small leak from the left atrial appendage, statistically significant perforation of the apex of the left ventricle. Death occurred (6 days after procedure) from septic shock and renal failure. In 3 cases the first valve implanted was too low, severe AR (grade 4) was seen. Second valve implant reduced AR (grade 1), peak and mean transaortic valve gradient decreased, but there was mild paravalvular AR. In 1 case a permanent pacemaker was needed, and an embolic stroke occurred on the day after the procedure.	Larger studies included in table 2.
Pasic M, Unbehaun A, Dreysse S et al. (2011) Transapical aortic valve implantation after previous aortic valve implantation: clinical proof of the “valve-in-valve” concept. Journal of Thoracic and	Prospective case series N=14 patients at high risk with degenerated biological aortic valve prosthesis Technique: ViV-TAVI	Procedural success was 100%. Preoperative TTE mean transvalvular gradient was reduced from 37.1 ± 25.7 mmHg to 13.1 ± 6.4 mmHg, and mean aortic valve area increased from 0.68 ± 0.23 cm2 to 1.35 ± 0.48 cm2. There	Larger studies included in table 2. Included in systematic reviews added to table 2 (Phan, Chen 2016).

Cardiovascular Surgery 142: 270–7.	Follow up: 2–20 months	was no postoperative valve insufficiency. The postoperative course was short and uneventful in all but 1 patient. One patient had reoperation 3 months later because of endocarditis. Up to 20 months postoperatively, the patients were in New York Heart Association functional class I or II.	
Pascual I, Avanzas P et al (2019). Self-expanding transcatheter aortic valve implantation for degenerated Mitroflow bioprosthesis: Early outcomes. International Journal of Cardiology (01) 01.	Case series N=45 VIV-TAVI with self-expandable valve in patients with degenerated bioprosthetic valves.	The STS predicted risk of mortality was 6.3+/-6.3%. The safety primary endpoint occurred in 4 patients (8.8%). The efficacy endpoint was present in all patients (100%). There were no coronary occlusions or procedural deaths. The number of patients with any degree of PPM raised from 51.1% (pre-TAVI) to 60% (post-TAVI).	Lager studies included in table 2.
Raval J, Nagaraja V et al (2014). Transcatheter valve-in-valve implantation: a systematic review of literature. Heart, Lung and Circulation, 23 (11), 1020–8.	Systematic review Valve-in-valve implantation using THVs in aortic, mitral, pulmonary, tricuspid positions. N=61 studies (31 studies ViV-TAVI, 13 studies mitral VIV, 12 studies tricuspid VIV and 9 studies native aortic valve regurgitation. Most studies were case series and case reports.	Valve-in-valve implantation can be considered as an acceptable alternative to conventional open-heart surgery for elderly high-risk surgical patients with bioprosthetic degeneration. Long-term follow up of patients who had treatment will be necessary to establish the true role of valve-in-valve implantation for bioprosthetic degeneration. Patients should be evaluated on an individual basis until outcomes are proven in large cohort studies or randomised trials.	More comprehensive and recent reviews added to table 2.
Reul RM, Ramchandani MK et al (2017). Transcatheter Aortic Valve-in-Valve Procedure in Patients with Bioprosthetic Structural Valve Deterioration. Methodist Dekakey Cardiovascular Journal, 13 (3): 132–41.	Review	Data from studies and analyses of results from clinical procedures have led to strategies to improve outcomes of VIV-TAVI procedures. The type, size, and implant position of the valve can be optimized for patients with knowledge of detailed dimensions of the surgical valve and radiographic and echocardiographic measurements of the patient's anatomy. Understanding the complexities of the ViV procedure can lead surgeons to make choices during the original surgical valve implantation that can make a future ViV operation more	Review

		technically feasible years before it is needed.	
Ribeiro HB, Rodes-Cabau J et al (2018). Incidence, predictors, and clinical outcomes of coronary obstruction following transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: insights from the VIVID registry. European Heart Journal (39) 8 687-695.	Case series (retrospective analysis) N=1612 VIV-TAVI (VIVID registry) 37 patients with coronary obstruction versus controls	A total of 37 patients (2.3%) had clinically evident coronary obstruction. Coronary obstruction was more common in stented bioprostheses with externally mounted leaflets or stentless bioprostheses than in stented with internally mounted leaflets bioprostheses (6.1% vs. 3.7% vs. 0.8%, respectively; P<0.001). CT measurements were obtained in 20 (54%) and 90 (5.4%) of patients with and without coronary obstruction, respectively. VTC distance was shorter in coronary obstruction patients in relation to controls (3.24 +/- 2.22 vs. 6.30 +/- 2.34, respectively; P<0.001). Using multivariable analysis, the use of a stentless or stented bioprosthesis with externally mounted leaflets [odds ratio (OR): 7.67; 95% confidence interval (CI): 3.14-18.7; P<0.001] associated with coronary obstruction for the global population. In a second model with CT data, a shorter VTC distance predicted this complication (OR: 0.22 per 1 mm increase; 95% CI: 0.09-0.51; P<0.001), with an optimal cut-off level of 4 mm (area under the curve: 0.943; P<0.001). Coronary obstruction was associated with a high 30-day mortality (52.9% vs. 3.9% in the controls, respectively; P<0.001).	Coronary obstruction reported in studies included in table 2.
Ruparelia N, Thomas K et al (2017). Transfemoral transcatheter aortic valve-in-valve implantation for aortic valve bioprosthesis failure with the fully repositionable and retrievable Lotus valve: a single-center experience. Journal of Invasive Cardiology 29, 9: 315–9.	Case series N=7 patients who had TF VIV-TAVI with Lotus valve for aortic bioprosthetic valve failure. Follow up: 30 days	Device success (VARC 2 definition) was achieved in 6/7 patients. Transvascular haemodynamics improved (mean 11.9mmHg). all patients had mild or no residual aortic regurgitation. No further compilations occurred.	Larger studies included in table 2.
Sang SLW, Beute T et al (2017). Early outcomes for valve-in-valve transcatheter aortic valve	Case series N=22 ViV-TAVR in degenerated	Device success using a self-expanding transcatheter valve was 95%, all via transfemoral approach. The mean implant	Larger studies included in table 2.

replacement in degenerative Freestyle bioprostheses. Seminars in Thoracic and Cardiovascular Surgery, 30 (3): 262–8.	Freestyle stentless bioprostheses. Follow up: 30 days	depth was 7 ± 3 mm.30-day survival was 100%. No patient had more than mild paravalvular regurgitation at 30 days, and the permanent pacemaker rate was 9%. The mean hospital stay after intervention was 5 ± 2 days.	
Sang SLW, Beute T et al (2018). Early Outcomes for Valve-in-valve Transcatheter Aortic Valve Replacement in Degenerative Freestyle Bioprostheses. Seminars in Thoracic & Cardiovascular Surgery (30) 3 262-268.	Retrospective analysis N=22 VIV-TAVI in degenerated Freestyle stentless bioprostheses.	Device success using a self-expanding transcatheter valve was 95%, all via transfemoral approach. The mean implant depth was 7 +/- 3 mm. 30-day survival was 100%. No patient had more than mild paravalvular regurgitation at 30 days, and the permanent pacemaker rate was 9%. The mean hospital stay after intervention was 5 +/- 2 days.	Lager studies included in table 2.
Santarpino G, Pietsch LE et al (2016). Transcatheter aortic valve-in-valve implantation and sutureless aortic valve replacement: 2 strategies for one goal in redo patients. Minerva Cardioangiologica, 64 (4) 581–5.	Retrospective case series N=14 patients with bioprosthetic AV degeneration had ViV-TAVI (n=6) and redo SAVR in sutureless valves (n=8) with Sapien valves. Follow up 21 months	There was no in-hospital death. No patient was lost to follow up. Quality of life improved by 65% in the sutureless group and by 67% in the ViV-TAVI group. At follow-up echocardiographic evaluation, no paravalvular leak or intraprosthetic regurgitation was observed in either group. The mean iEOA was 0.96±0.08 versus 0.71±0.15 cm2/m2 in the sutureless versus ViV-TAVI group.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Tam, Gozdek 2018).
Salaun E, Zenses A. S et al (2019). Valve-in-Valve Procedure in Failed Transcatheter Aortic Valves. Jacc: Cardiovascular Imaging (12) 1 198-202.	Review of 5 cases		Review
Schaefer A, Deuschl F et al (2018). Valve-in-valve-in-valve: Balloon expandable transcatheter heart valve in failing self-expandable transcatheter heart valve in deteriorated surgical bioprosthesis. Catheterization & Cardiovascular Interventions (92) 7 E481-E485.	Case report N=81-year-old female patient with surgical aortic valve replacement was treated by ViV because of deterioration.	A second ViV procedure with initial intentional rupture of the bioprosthetic stent was performed. Immediate stent recoil of the Evolut R prompted implantation of a Sapien 3. In 30-day follow up, mean pressure gradient of 30 mmHg and nearly complete symptom relief was seen. Supra-annular placement of a balloon-expandable THV as ViV-in-valve is feasible with suboptimal hemodynamic results in this case.	Lager studies included in table 2.

Schwerg M, Stangl K et al (2018). Valve in valve implantation of the CoreValve Evolut R in degenerated surgical aortic valves. Cardiology Journal 25, 3: 301–7.	Case series N=26 patients had VIV-TAVI (CoreValve ER) for degenerated aortic bioprosthetic valves. Follow up: 30 days	Implantation was successful in all. The mean transaortic gradient for stenotic valves was reduced statistically significantly from 37.5 ± 15.3 mmHg in patients with prosthesis stenosis to 16.3 ± 8.2 mmHg ($p<0.001$). In cases with severe prosthesis regurgitation, regurgitation was reduced to none or mild. All-cause mortality after 30 days was 0%.	Larger studies included in table 2.
Scholtz S, Piper C et al (2018). Valve-in-valve transcatheter aortic valve implantation with CoreValve/Evoult R for degenerated small versus bigger prostheses. Journal of Interventional Cardiology. 31 (3), DOI: [10.1111/joic.12498](https://doi.org/10.1111/joic.12498)	Case series N=37 patients with degenerated bioprostheses had ViV-TAVI (CoreValve/Evoult R). Follow up: 3 years	Successful valve implantation in all, a permanent pacemaker was implanted in 16% cases, no strokes or coronary obstructions were reported. Mortality at 30 days was 2.7%, at 1 year 5.7% and at 3 years 13.5%. Depending on bioprosthesis size<23mm versus>23mm, echocardiographic gradients were significantly higher in the smaller prostheses post implantation (22.8mmHg versus 15.1mmHg, $p=0.013$).	Larger studies included in table 2.
Seiffert M, Coradi L, Baldus S et al. (2012) Impact of patient-prosthesis mismatch after transcatheter aortic valve-in-valve implantation in degenerated bioprostheses. Journal of Thoracic and Cardiovascular Surgery 143: 617–24.	Case series (retrospective) 11 patients with severe degeneration of implanted xenograft bioprostheses Technique: ViV-TAVI Follow up: 6 months or 1 year	Severe PPM was evident in 5 patients (group 1 iEOA<0.65 cm^2/m^2) and absent in 6 patients (group 2 iEOA>0.65 cm^2/m^2). Mean transvalvular gradients decreased from 29.2 ± 15.4 mmHg before implantation to 21.2 ± 9.7 mmHg at discharge (group 1) and from 28.2 ± 9.0 mmHg before implantation to 15.2 ± 6.5 mmHg at discharge (group 2). Indexed effective orifice area increased from 0.5 ± 0.1 cm2/m2 to 0.6 ± 0.1 cm2/m2 and from 0.6 ± 0.3 cm2/m2 to 0.8 ± 0.3 cm2/m2. Aortic regurgitation decreased from grade 2.0 ± 1.1 to 0.4 ± 0.5 overall. No differences in New York Heart Association class improvement or survival during follow up were observed. One patient needed reoperation for symptomatic PPM 426 days after implantation.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Phan, Chen 2016).
Seiffert M, Franzen O, Conardi L et al. (2010). Series of transcatheter valve-in-valve implantation in high-risk patients with	Case series n=5 Follow up=30 days	Mean transvalvular gradient reduced from 31.2 ± 17.4 mmHg. No statistically significant AR.	ViV in aortic (4) and mitral (1) position.

degenerated bioprostheses in aortic and mitral position. Catheter Cardiovascular Interventions 76: 608–15.	Degenerated xenografts. ViV-TA approach 23 mm Edwards Sapien valve	2 patients died because of low-cardiac output and acute haemorrhage (one had Logistic EuroSCORE 89%).	Safety results not reported separately. Larger studies included in table 2.
Silaschi M, Wendler O et al (2017). Transcatheter valve-in-valve implantation versus redo surgical aortic valve replacement in patients with failed aortic bioprostheses. Interact CardioVasc Thorac Surg; 24:63–70.	Retrospective comparative case series N=130 patients with failed aortic bioprostheses. ViV: n=71, redo-SAVR: n=59 Follow up: 180 days	The 30-day mortality rate was not significantly different (4.2% and 5.1% respectively; p=1.0). Device success was achieved in 52.1% (ViV) and 91.5% (P<0.01). No stroke was observed after ViV but in 3.4% after redo-SAVR (p=0.2). Intensive care stay was longer after redo-SAVR (3.4 ± 2.9 versus 2.0 ± 1.8 days, p<0.01). Mean transvalvular gradients were higher post-ViV (19.7 ± 7.7 versus 12.2 ± 5.7 mmHg, P<0.01), whereas the rate of permanent pacemaker implantation was lower (9.9 versus 25.4%, p<0.01). Survival rates at 90 and180 days were 94.2 and 92.3% versus 92.8 and 92.8% (p=0.87), respectively.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Tam, Gozdek 2018).
Soulami RB, Verhoye JP et al (2016). Computer-assisted transcatheter heart valve implantation in valve-in-valve procedures. Innovations 11: 193–200.	Case series N=9 computer-assisted VIV.	The VIV procedures into degenerated were successful and reproducible.	Preliminary feasibility study.
Souza RC, Paim L et al (2018).Thrombocytopenia After Transcatheter Valve-in-Valve Implantation: Prognostic Marker or Mere Finding? Brazilian Journal of Cardiovascular Surgery (33) 4 362-370.	Retrospective case series N=28 patients with ViV (5 aortic valve, 18 mitral, 5 tricuspid positions). Compared with 74 conventional redo valvular replacements.	All VIV patients developed thrombocytopenia, 25% mild (<150.000/micro L), 54% moderate (<100.000/micro L) and 21% severe (<50.000/micro L) thrombocytopenia. The aortic subgroup comparison between VIV and conventional surgery showed a statistically significant difference from the 7th day, where VIV patients had more severe and longer lasting thrombocytopenia. This, however, did not translate into a higher postoperative risk/ occurrence of adverse outcomes.	VIV in positions other than aortic also included.
Spaziano M, Mylotte D et al (2017). Transcatheter aortic valve implantation versus redo surgery for failing surgical aortic	Retrospective propensity score matched study VIV-TAVI=79 versus	All-cause mortality was similar between groups at 30 days (6.4% redo-SAVR versus 3.9% TAV-in-SAV; p=0.49) and 1 year (13.1% redo-SAVR	Larger studies included in table 2. Included in systematic reviews added to

bioprostheses: a multicentre propensity score analysis. EuroIntervention;13:1149–56.	Redo SAVR=126 78 matched pairs included Follow up=1 year	versus 12.3% TAV-in-SAV; p=0.80). Both groups also showed similar incidences of stroke (0% redo-SAVR versus 1.3% TAV-in-SAV; p=1.0) and new pacemaker implantation (10.3% redo-SAVR versus 10.3% TAV-in-SAV; p=1.0). The incidence of acute kidney injury needing dialysis was numerically lower in the TAV-in-SAV group (11.5% redo-SAVR versus 3.8% TAV-in-SAV; p=0.13). The TAV-in-SAV group had a significantly shorter median total hospital stay (12 days redo-SAVR versus 9 days TAV-in-SAV; p=0.001).	table 2 (Tam, Gozdek 2018).
Stahli BE, Reinthaler M et al (2014). Transcatheter aortic valve-in-valve implantation: clinical outcome as defined by VARC-2 and postprocedural valve dysfunction according to the primary mode of bioprosthesis failure. The Journal of Invasive Cardiology. 26, 10: 542–7.	Retrospective case series N=14 patients at high risk with failed aortic surgical bioprostheses had VIV-TAVI Follow up=mean 1 month	Successful implantation in 93% (13/14). In 1 patient a second transcatheter valve was implanted because of valve malpositioning. 30-day all-cause mortality was 7% (1/14). Prosthetic valve dysfunction at 30 days was seen in 50% (7/14) patients because of an increased post-procedural transvalvular gradient>20mmHg. At 30 days follow up, post-procedural transaortic gradients were higher in patients with aortic stenosis as compared to those with aortic regurgitation (36mmHg versus 16mmHg; p=0.1). None reported valve regurgitation of more than mild degree.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Phan 2016).
Stankowski T, Aboul-Hassan SS et al (2019). Severe structural deterioration of small aortic bioprostheses treated with valve-in-valve transcatheter aortic valve implantation. Journal of Cardiac Surgery (34) 1 7-13.	Case series N=27 patients at high risk who had TF VIV-TAVI for degenerated small bioprostheses (19-21mm) Follow up was 3.2 +/- 2.0 years.	Early mortality was 11.1%. 1 patient died intraoperatively because of left ventricle perforation, 2 others during in-hospital as a result of sudden cardiac death and pulmonary embolism. VIV-TAVI was completed in 26 cases (96.3%-success rate). 2 patients required pacemaker implantation. Acute kidney injury occurred in 2 other patients. At discharge, mean transvalvular gradient was 19.2 +/- 9.5 mmHg and in 25.9% of patients mean gradient exceeded 20 mmHg. Overall mortality was 25.9% and mortality from cardiac or	Larger studies included in table 2.

		unknown causes at 18.5%. 90% of survivors were in New York Heart Association (NYHA) class I or II.	
Subban V, Savage M et al (2014). Transcatheter valve-in-valve replacement of degenerated bioprosthetic aortic valves: a single Australian Centre experience. Cardiovascular Revascularization Medicine, 15: 388–92.	Retrospective case series N=12 patients with degenerated bioprosthetic aortic valves had VIV-TAVI Follow up=mean 26 months.	Successful deployment without major valvular or paravalvular regurgitation in all. There were no periprocedural deaths, myocardial infarcts, neurological events or major vascular complications. 2 patients died after 1624 and 1319 days. Median survival was 581 days, stable with NHYA class I/II functional status, 4 have a degree of patient–prosthesis mismatch, 1 had moderate aortic regurgitation and 1 needed surgery for a late aortic dissection.	Larger studies included in table 2. Included in systematic reviews added to table 2 (Phan 2016).
Summers MR, Mick S et al (2018). Emergency valve-in-valve transcatheter aortic valve replacement in a patient with degenerated bioprosthetic aortic stenosis and cardiogenic shock on veno-arterial extracorporeal membrane oxygenation. Catheterization & Cardiovascular Interventions (92) 3 592-596.	Case report	We describe herein a unique case in which ViV-TAVR was successfully used as both an emergency salvage therapy and a bridge to definitive fourth reoperative aortic valve replacement in a young patient with cardiogenic shock secondary to bioprosthetic aortic valve stenosis who was dependent on veno-arterial extracorporeal membrane oxygenation (VA-ECMO).	Lager studies included in table 2.
Szlapka M, Michel E et al (2018). Valve-in-valve-prosthesis embolization and aortic dissection: single procedure, double complication. European Journal of Cardiothoracic Surgery (14) 14.	Case report A 73-year-old woman presented with structural valve degeneration 14 years after aortic root replacement with a bioprosthetic valved conduit. The patient had VIV-TAVI	Intraoperatively, the self-expandable prosthesis was difficult to deploy within the valved conduit and ultimately migrated distally. During the technically difficult passage of the prosthesis delivery system through the tortuous aorta, the patient started reporting symptoms suggestive of aortic dissection. An emergency computed tomography scan confirmed type B dissection. Thoracic endovascular aortic repair followed by deployment of a balloon-expandable prosthesis below the self-expandable implant was performed.	Lager studies included in table 2.
Toggweiler S, Wood DA et al (2012). Transcatheter valve-in-valve implantation for failed balloon-	Retrospective case series	Procedure was successful in 19 patients (90%). Mortality at 30 days and 1 year was 14.3% and 24%, respectively. Post-	Larger studies included in table 2

expandable transcatheter aortic valves. JACC Cardiovascular Interventions. 5:571–7.	N=21 patients had a ViV-TAVI implant because of acute severe regurgitation. Follow up: 12 months	implantation mean aortic valve gradient fell from 37 ± 12 mmHg to 13 ± 5 mmHg (p<0.01); aortic valve area increased from 0.64 ± 0.14 cm2 to 1.55 ± 0.27 cm2 (p<0.01); and paravalvular aortic regurgitation was none in 4 patients, mild in 13 patients, and moderate in 2 patients. At 1-year follow up, 1 patient had moderate and the others had mild or no paravalvular leaks. The mean transvalvular gradient was 15 ± 4 mmHg, which was higher than in patients having conventional TAVR (11 ± 4 mmHg, p=0.02).	
Tourmousoglou C, Rao V, Lalos S, Dougenis D (2015). What is the best approach in a patient with a failed aortic bioprosthetic valve: transcatheter aortic valve replacement or redo aortic valve replacement? Interact CardioVasc Thorac Surg;20:837–43.	Systematic review ViV-TAVI versus redo SAVR for degenerative bioprosthetic aortic valve (12 retrospective studies: 4 on redo SAVR, 6 on ViV-TAVI and 2 propensity matched studies between ViV-TAVI and redo SAVR)	30-day mortality for rAVR was 2.3–15.5% and 0–17% for VIV-TAVR. For rAVR, survival rate at 30 days was 83.6%, 76.1% at 1 year, 70.8% at 3 years, at 51.3–66% at 5 years, 61% at 8 years and 61.5% at 10 years. For viv-TAVR, the Kaplan–Meier survival rate at 1 year was 83.2%. After VIV-TAVR at 1 year, 86.2% of patients were at NYHA class I/II. The complications after rAVR were stroke (4.6–5.8%), reoperation for bleeding (6.9–9.7%), low-cardiac output syndrome (9.9%) whereas complications after viv-TAVR at 30 days were major stroke (1.7%), aortic regurgitation of moderate degree (25%), permanent pacemaker implantation rate (0–11%), ostial coronary obstruction (2%), implantation of a second device (5.7%) and major vascular complications (9.2%). ViV-TAVI is effective in the short term and redo aortic valve replacement achieves acceptable medium and long-term results. Both techniques are complementary approaches for patients at high risk with degenerative bioprosthetic valves.	More recent comprehensive reviews included in table 2.
Ye J, Cheung A et al (2015). Transcatheter Aortic and Mitral Valve-in-Valve Implantation for Failed Surgical Bioprosthetic Valves: An	Case series N=73 patients with aortic (n=42) and mitral (n=310 bioprosthetic valve dysfunction had	72 patients had successful VinV had (success rate 98.6%). At 30 days, all-cause mortality was 1.4%, disabling stroke 1.4%, life-threatening bleeding 4.1%, acute kidney	Larger studies included in table 2. Included in Chen 2016 added to table 2.

8-Year Single-Center Experience. JACC: Cardiovascular Interventions 8 (13) 1735–44.	ViV-TAVI (Edwards balloon-expandable THV). Median follow up 2.52 years, maximum 8 years.	injury needing haemodialysis 2.7%, and coronary artery obstruction needing intervention 1.4%. No patient had greater than mild paravalvular leak. Estimated survival rates were 88.9%, 79.5%, 69.8%, 61.9%, and 40.5% at 1, 2, 3, 4, and 5 years, respectively. The small surgical valve size (19 and 21 mm) was an independent risk factor for reduced survival in aortic VinV patients. At 2-year follow up, 82.8% of aortic and 100% of mitral VinV patients were in New York Heart Association functional class I or II.	
Ye J, Webb JG et al (2013). Transapical transcatheter aortic valve-in-valve implantation: Clinical and hemodynamic outcomes beyond 2 years. The Journal of Thoracic and Cardiovascular Surgery 145 (6), 1554–62.	Case series N=8 patients had ViV-TAVI (Edwards SAPIEN) into failed aortic surgical bioprosthesis. Follow up: mean 27.8 months	Procedure was successful in all. The predicted operative mortality was 42.1% ± 15.7% by logistic EuroSCORE and 14.4% ± 9.6% using the STS risk calculator. The observed 30-day mortality was 12.5%. No strokes or valve embolisation/migrations occurred. The New York Heart Association class decreased from preoperative class III-IV to postoperative class I in 6 of 7 survivors. The 2-year survival was 87.5%. No late mortality occurred during the follow-up period. The echocardiographic results at 1 to 4 years showed stable valve position and function in all patients. The transaortic valve pressure gradients after implantation were greater than 20 mmHg and less than 15 mmHg in patients with 21- or 23-mm and 25-mm surgical valves, respectively.	Larger studies included in table 2.
Stenotic prosthesis after TAVI-Rescue			
Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. Circulation 2010;121:1848–57.	Case series n=10 aortic viv median 135 days	The first published case series of valve-in-valve procedures, including TAV implantation for failing aortic, mitral, pulmonary and tricuspid bioprostheses.	Larger studies included in table 2.
Webb JG. and Dvir D (2013). Transcatheter aortic valve replacement for bioprosthetic aortic valve failure: the valve-in-valve procedure. [Review].		TAVI within failed surgically implanted bioprosthetic valves has proven feasible. Potential and challenges of valve-in-valve implantation in patients	Review

Circulation 127 (25) 2542–50.		with failing surgical aortic bioprosthesis.	
Wilbring M, Alexiou K, Tugtekin SM et al (2013). Transcatheter valve-in-valve therapies: patient selection, prosthesis assessment and selection, results, and future directions. [Review]. Current Cardiology Reports 15 (3) 341.		Valve-in-valve TAVI seems to be safe and effective in treatment of deteriorated valve prostheses in patients at high risk. The valve-in-valve concept presents the next step towards an individual treatment strategy for patients at prohibitive risk for conventional surgery. Present studies were reviewed with special concern to patient selection, prosthesis assessment, device selection, clinical outcome and technical challenging aspects as well.	Review
Wilbring M, Sill B, Tugtekin SM et al. (2012). Transcatheter Valve-in-Valve implantation for deteriorated aortic bioprosthesis: Initial clinical results and follow-up in a series of high risk patients. Annals of Thoracic Surgery 93: 734–41.	Case series n=7 Follow up: 15.3 months (median) range 9 to 26 months. TA-ViV implantation Device: Edwards Sapien 23 or 26 mm Patients with deteriorated aortic valve bioprosthesis (6 patients with symptomatic stenosis and 1 patient with severe valvular insufficiency).	Procedural success -100%. No procedural complications. Improvement in haemodynamic function. Postoperative complications: Mild acute kidney injury (n=3), transient bradycardia with no pacemaker implant (n=1), respiratory failure by pre-existing COPD (n=2), transient symptomatic psychotic syndrome (n=2). No patients died, transvalvular gradients decreased in all except 1 patient. NYHA functional class improved in all except 1 patient in class III with defibrillator, who had recurrent episodes of heart failure, dislocation of defibrillator and was hospitalised. In 1 patient at discharge elevated peak and mean pressure gradients and severe left ventricular hypertrophy and systolic occlusion of the left cavum in accordance with volume depletion were seen.	Larger studies included in table 2.
Witkowski A, Jastrzebski J et al (2014). Second Transcatheter Aortic Valve Implantation for Treatment of Suboptimal Function of Previously Implanted Prosthesis: Review of the Literature. J Interv Cardiol , 27 (3), 300-307.	To systematically review reported cases of second transcatheter aortic valve deployment within a previously implanted prosthesis (TAV-in-TAV).	43 articles on TAV-in-TAV deployment were included in the review. The most frequently observed indication for second valve implantation was aortic regurgitation (AR) occurring shortly after TAVI. There was a strong dominance of paravalvular over intravalvular AR, with prosthesis malposition being the main underlying cause of TAVI failure (81% of all	Studies reported in this review are already included in table 2.

		identified cases). Perioperative echocardiographic images are crucial in identifying causes of failure and helpful in optimal rescue strategy selection. Success rate of TAV-in-TAV implantation varies from 90% to 100% with mortality rate of 0-14.3% at 30 days. Despite similar aortic valve function in follow up, TAV-in-TAV may be an independent predictor of increased cardiovascular mortality. **CONCLUSIONS:** TAV-in-TAV implantation is feasible and results in favourable short- and mid-term outcomes in patients with acute failure of TAVI without recourse to open-heart surgery. Further studies are needed to establish algorithm of the management of unsuccessful or suboptimal implantation results.	
Wernly B, Zappe AK et al (2019). Transcatheter valve-in-valve implantation (VinV-TAVR) for failed surgical aortic bioprosthetic valves. Clinical Research in Cardiology (108) 1 83-92**.**	n=223 patients with failed surgical aortic bioprosthetic valves had VinV-TAVR	TAVR was associated with high procedural success rate, conversion to surgery was necessary in 3 (2%) patients. After VinV-TAVR procedure, 4 (2%) patients suffered from>=moderate AR. In 6 (3%) patients a second valve was implanted because mispositioning of the first valve and subsequent severe paravalvular AR. Coronary obstruction was observed in 4 (2%) patients. Major bleeding and cerebrovascular complications (according to VARC) were reported in 3 (1%) and 4 (2%) patients at 30 days. Post-interventionally, 44/178 (25%) patients evidenced a mean pressure gradient (mPG)>=20 mmHg. Residual stenosis was not associated with increased mortality (HR 0.39; 95% CI 0.13-1.22; p=0.11).	Lager studies included in table 2.