NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve

A paravalvular leak is when blood leaks around a replacement heart valve. It can cause symptoms of heart failure such as shortness of breath and swelling in the feet and legs. In this procedure, a small tube (catheter) is put into a large vein (for a mitral valve) or artery (for an aortic valve), typically at the top of the leg (percutaneous). A wire is guided through the catheter to the heart valve. Then a device is passed through the catheter and used to block the area that is leaking. The aim is to stop the leak.

Contents

Appendix

Abbreviations

Word or phrase	Abbreviation
Aortic valve leak	AL
Confidence interval	CI
Hazard ratio	HR
Mitral valve leak	ML
New York heart association	NYHA
Odds ratio	OR
Paravalvular leak	PVL
Paravalvular leak device	PLD
Percutaneous	P
Standard deviation	SD
Surgical	S
Transoesophageal echocardiography	TEE

Introduction

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

Date prepared

This overview was prepared in August 2020 and updated in February 2021.

Procedure name

- Percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve

Professional societies

- Society of Cardiothoracic Surgery of Great Britain and Ireland
- British Cardiovascular Intervention Society
- British Cardiac Society.

Description of the procedure

Indications and current treatment

Paravalvular leak is a complication after surgical or transcatheter replacement of a mitral or aortic valve. Most leaks are not significant, but some leaks may lead to heart failure or haemolytic anaemia.

Current treatments include a second surgical procedure to replace the malfunctioning valve or valve-in-valve transcatheter aortic valve insertion.

What the procedure involves

The procedure is done using a combination of local anaesthetic and sedation, or general anaesthesia. The exact technique varies according to the type of leak being repaired.

For mitral valves, an antegrade transseptal approach is most commonly used. In this approach, transseptal left atrial catheterisation is done under imaging guidance using standard techniques. A guidewire may be used to cross the leak. A delivery sheath is then passed from the venous access and 1 or more closure devices are deployed to close the leak. Transoesophageal echocardiography is used to confirm adequate reduction of peri-mitral regurgitation and fluoroscopy used to confirm normal mechanical prosthetic leaflet motion before closure device release.

For aortic valves, a retrograde approach is usually used. Transthoracic echocardiography may be enough to image the leak, but for posterior leaks, transoesophageal echocardiography or intracardiac echocardiography may be needed. The leak is usually crossed using a guidewire over a catheter. After crossing, the guidewire is exchanged for a stiffer wire and a delivery sheath is advanced to deploy the closure device.

More than 1 device may be needed to adequately close the leak. Different devices are available for use in this procedure.

Efficacy summary

Technical success

In a systematic review and meta-analysis of 2,373 patients comparing 1,511 patients who had mitral or aortic percutaneous closure with 862 patients who had surgical repair of paravalvular leaks (PVLs), the technical success rate was statistically significantly lower for patients who had percutaneous closure (72.1% versus 96.7%, OR 9.7, 95% confidence interval [CI] [5.48 to 17.08], $p<0.001$, $I^2 = 67,8\%$). Mitral valve leak was the most common location in this meta-analysis (74% of included patients).[1]

In a non-randomised study of 381 patients with mitral PVL comparing percutaneous closure (n=195) with surgical repair (n=186), the technical success rate was statistically significantly lower for percutaneous closure (70.1% versus 95.5%, $p<0.001$).[2]

In a non-randomised study of 87 patients with PVL comparing percutaneous closure (n=46) with surgical closure (n=41), the technical success rates were not statistically significantly different between groups (83% compared with 90%, p=0.303). [3]

In a retrospective Spanish registry of 469 patients who had percutaneous PVL closure, the technical success rate (defined as successful delivery of a PVL closure device without interference with the valve prosthesis) was 87% and the procedural success rate was 73% (defined as technical success and 1 or more than 1 grade regurgitation reduction).[4]

In a retrospective UK and Irish registry of 259 patients who had percutaneous PVL closure, devices were successfully implanted in 91% of patients, via radial (7%), femoral arterial (52%), femoral venous (33%), and apical (7%) approaches. [5]

In a retrospective registry of 136 patients who had percutaneous PVL closure, the device success rate (defined as patients with stable implantation and paravalvular regurgitation reduced to small or less) at day of implantation was 89% (95% CI 80% to 94%) and the procedural success rate (defined as device success and no procedure- or device-related major complication) at day of implantation was 87% (95% CI 77% to 93%]. [6]

In a case series of 200 patients who had percutaneous PVL closure, the device was successfully deployed in 92% (184/200) of patients and the procedural success rate was 89% (178/200). The reasons for procedural failure included: 8 prosthetic leaflet impingements, 6 devices deployed with residual severe regurgitation, 5 device embolisations, 3 inability to cross with guidewire, 2 inability to cross with delivery sheath and 1 coronary dissection.[7]

In a non-randomised study of 131 patients comparing percutaneous closure (n=68) with surgical repair (n=63), the procedural success rate (defined as proper deployment of the device that resulted in significant reduction in regurgitation to mild-to-moderate or less residual regurgitation, without interference with the prosthesis or need for emergent surgery) was 98% (67/68). [8]

Clinical success rate and improvement in NYHA heart failure classification

In the systematic review and meta-analysis of 2,373 patients, there was no statistically significant difference in the improvement in NYHA classification for heart failure between the percutaneous and surgical groups (56% compared with 67.4%, odds ratio [OR] 1.37, 95% CI [0.21 to 8.94], p=0.74, I^2=91.5%).[1]

In the non-randomised study of 87 patients comparing percutaneous closure with surgical closure, the clinical success rates (defined as an improvement of at least one NYHA functional class with no rehospitalisation or reinterventions for the index reason) were not statistically significantly different between groups at 5 years (70% compared with 73%, p=0.711).[3]

In the retrospective UK and Irish registry of 259 patients, the mean NYHA class statistically significantly improved from 2.7±0.8 before the procedure to 1.6±0.8 over a median follow up of 110 days(range 7 to 452 days) (p<0.001). There were less patients with NYHA class 4 and 3 after the procedure (decrease from 15% to 3% for NHYA class 4 and from 52% to 8% for NYHA class 3). There were more patients with NYHA class 2 or 1 after the procedure (increase from 26% to 40% for NHYA class 2 and an increase from 7% to 50% for NYHA class 1). [5]

In the retrospective registry of 136 patients, the clinical success rate at 6 months (defined as patients in NYHA Class 1 or 2 or patients no longer dependent on blood transfusions at 6 months, who did not experience procedure- or device-related major complications) was 87% (95% CI 79% to 92%). In the same study, NYHA classification improved statistically significantly after closure for both mitral and aortic PVLs (p<0.0001). The proportion of patients with NYHA Class 3 or 4 decreased from 77% at baseline to 17% at latest follow up.[6]

In the non-randomised study of 131 patients, there were more patients with an NYHA class improvement of 1 or more at 1-year follow up for percutaneous

closure than for surgical repair (82% [55/67] compared with 68% [39/57], no level of statistical significance reported).[8]

Long-term survival

In the non-randomised study of 87 patients, the overall survival rates at 5 years were not statistically significantly different between groups (74% compared with 72%, p=0.451). Cardiac-related survival at 5 years was not statistically significantly different between groups either (84% compared with 75%, p=0.192).[3]

Residual leak

In the non-randomised study of 381 patients, there were no residual leak in 40% (78/195) of patients who had percutaneous closure compared with 83% (128/186) of patients who had surgical closure. There were mild residual leaks (grade 1) in 30% (58/195) of patients who had percutaneous closure compared with 13% (20/186) of patients who had surgical closure; moderate residual leaks (grade 2) for 19% (36/195) compared with 3% (5/186) and severe residual leaks (grade 3) for 11% (22/195) compared with 1% (2/186) of patients for percutaneous and surgical closure respectively (p<0.001).[2]

In the non-randomised study of 87 patients, 15% (7/46) of patients who had percutaneous closure had a residual obvious PVL at discharge compared with 2% (1/41) of patients who had surgical closure (no statistically significant difference between groups, p=0.061). The residual obvious PVLs in transcatheter group included unable to cross the defect (n=2), prosthetic impingement (n=1), significant residual PVL after devices deployed (n=4).[3]

In the retrospective UK and Irish registry of 259 patients, there was a statistically significant improvement in the severity of PVLs following closure (p<0.001). There were 61% of patients with severe leaks before the procedure compared with 7% of patients after the procedure. Moderate leaks decreased from 34% to 19%, mild leaks increased from 6% to 41% and the absence of leaks increased from 0% to 33%. [5]

In the retrospective registry of 136 patients, PVL improved statistically significantly after closure for both mitral and aortic PVLs (p<0.0001). One patient had a repeat closure 4 months after the index procedure for significant residual leak.[6]

In the non-randomised study of 131 patients, PVL regurgitation was decreased to mild and mild to moderate immediately after the procedure in all patients who had percutaneous closure. There was a statistically significant decrease in the mean

volume of PVL regurgitation from 10.1± 2.9 ml before the procedure to 1.6 ml ± 1.7 ml after the procedure (p<0.01).[8]

Reintervention

In the systematic review and meta-analysis of 2,373 patients, there was no statistically significant difference in the reoperation rates between the percutaneous and surgical groups (9.9% compared with 9.1%, OR 0.72, 95% CI [0.49 to 1.06], p=0.1, I^2=36.1%).[1]

In the non-randomised study of 381 patients, there were no statistically significant differences between percutaneous and surgical closure for reintervention (11% (22/195) compared with 17% (32/186), p=0.10) and for reoperation (10% (20/195) compared with 10% (19/186), p=0.88). However, the repeat percutaneous intervention rate was statistically significantly lower for percutaneous closure (3% (5/195)) compared with 9% (17/186) for surgical closure (p=0.006). In the same study, the mean time to reintervention was statistically significantly shorter for percutaneous closure (6.2 ± 7.4 months compared with 42.8 ± 43.8 months for surgical closure, p<0.001). [2]

Re-hospitalisation within 5-year follow up was reported in 11% (5/45) of patients who had percutaneous closure compared with 14% (5/35) of patients who had surgical closure in the non-randomised study of 87 patients (no statistically significant difference between groups, p=0.670).[3]

In the retrospective registry of 136 patients, the need for a repeat procedure was reported in 1 patient. [6]

In the case series of 200 patients, elective cardiac surgery for unsuccessful repair was reported in 2% (3/200) of patients. [7]

Readmission for heart failure

In the systematic review and meta-analysis of 2,373 patients, the readmission rates for heart failure were similar for percutaneous closure and surgical repair of PVLs (26.4% versus 13.0%, OR 0.51, 95% CI [0.15 to 1.77], p=0.29, I^2=81.1%).[1]

Improvement of haemolytic anaemia

In the retrospective registry of 136 patients, the proportion of patients who needed a blood transfusion because of haemolysis decreased from 37% before the procedure to 6% after 6 months for mitral valves and from 8% before the procedure to none after 6 months for aortic valves. [6]

Hospital length of stay

In the systematic review and meta-analysis of 2,373 patients, the hospital length of stay was statistically significantly shorter for patients who had percutaneous closure compared with patients who had surgical repair of a PVL (standardised difference in mean –0.832, 95% CI [–0.976 to –0.689], p<0.001, I^2 = 53.9%).[1]

In the non-randomised study of 381 patients, the mean hospital length of stay was statistically significantly shorter for percutaneous closure (5.3 ± 7.6 days) compared with surgical closure (14.0 ± 11.0 days), p<0.001. [2]

In the non-randomised study of 87 patients, the mean hospital length of stay was statistically significantly shorter for percutaneous closure (12.42 ± 13.20 days) compared with surgical closure (29.57±24.65 days, p=0.003). [3]

In the non-randomised study of 131 patients, the mean hospital length of stay was statistically significantly shorter for percutaneous closure (7.9 ± 5.3 days) compared with surgical closure (38.1 ± 42.2 days), p=0.002. The mean length of stay in ICU was also statistically significantly shorter for percutaneous closure (0 compared with 4.3 ± 2.1 days, p<0.001). [8]

Safety summary

Death

In-hospital death

In-hospital death rate was statistically significantly lower for percutaneous closure in a non-randomised study of 381 patients with mitral PVL comparing percutaneous closure (n=195) with surgical repair (n=186): 3% (6/195) compared with 9% (16/186), p=0.027. [2]

The in-hospital death rate was statistically significantly lower for percutaneous closure in a non-randomised study of 87 patients with PVL comparing percutaneous closure (n=46) with surgical closure (n=41); 2% (1/46) compared with 15% (6/41), p=0.048. In the percutaneous group, the patient died from acute renal insufficiency secondary to acute haemolysis 6 days after the procedure.[3]

In a retrospective UK and Irish registry of 259 patients who had percutaneous PVL closure, the overall hospital mortality rate was 4%. There was a statistically significant difference in the hospital mortality rates between elective procedures (3%), in-hospital urgent procedures (7%) and emergency procedures (50%), p<0.001.[5]

The in-hospital mortality rate was statistically significantly lower in the percutaneous group in a non-randomised study of 131 patients comparing percutaneous closure (n=68) with surgical repair (n=63): 0% compared with 10% (6/63), p<0.001. [8]

In-hospital death was reported in 1 patient in a case series of 45 patients who had percutaneous PVL closure (also reported below). [9]

30-day mortality

30-day mortality rates were statistically significantly lower in patients having percutaneous closure compared with patients having surgical repair of PVLs in a systematic review and meta-analysis of 2,373 patients (1,511 versus 862): 6.8% versus 8.6%, OR 1.90, 95% CI [1.33 to 2.73], p<0.001, I^2=0%. [1]

All-cause death within 30 days of the procedure was reported in 5% (21/469) of patients in a retrospective Spanish registry of 469 patients who had percutaneous PVL closure.[4]

Death within 30 days of the procedure was reported in 2% (4/200) of patients in a case series of 200 patients who had percutaneous PVL closure. One patient died from sudden death, 1 patient died from cardiac tamponade and 2 patients died from sepsis. [7]

1-year mortality

One-year mortality rates were not statistically significantly different between patients having percutaneous closure and patients having surgical repair of PVLs in the systematic review and meta-analysis of 2,373 patients (17.2% versus 17.3%, OR 1.07, 95% CI [0.79 to 1.44], p=0.67, I^2=0%). [1]

Overall mortality

The overall mortality rate over a mean follow up of 4 years was statistically significantly lower for percutaneous closure in the non-randomised study of 381 patients (50% (98/195) compared with 68% (127/186) for surgical closure, p<0.001). After risk adjustment, there was no statistically significant difference in long-term survival between patients who had percutaneous compared with surgical treatment of PVLs (p=0.16).[2]

The death rates over a 5-year follow up were not statistically significantly different between groups in the non-randomised study of 87 patients: 18% (8/45) compared with 14% (5/35), p=0.675. In the percutaneous group, 4 patients died from severe post-procedure haemolysis within 1 year of hospital discharge and

4 patients died from non-cardiac causes (2 from severe pneumonia, 1 from suicide, and 1 from warfarin-related lower intestinal haematorrhea).[3]

Death was reported in 16% of patients over a median follow up of 110 days in the retrospective UK and Irish registry of 259 patients.[5]

All-cause mortality rate was 7% (10/136) in a retrospective registry of 136 patients who had percutaneous PVL closure. The causes of death were related to the disease in 6 patients, stroke death in 2 patients, sudden unexplained death in 1 patient and death after surgical valve replacement in 1 patient. [6]

There were 3 deaths during follow up in the patients (n=68) who had percutaneous closure (1 from recurrent haemolysis 5 months after the procedure, 1 from no specific reason 6 months after the procedure and 1 from heart failure 6 months after the procedure) compared with 4 deaths in the patients (n=63) who had surgical repair (2 from heart failure 12 and 20 months after the operation and 2 after a third open-heart operation for severe haemolysis because of recurrent paravalvular regurgitation) in the non-randomised study of 131 patients. [8]

Death was reported in 7% (3/45) of patients in the case series of 45 patients; 2 happened during follow up (no more details reported). [9]

Major adverse events

The rate of in-hospital major adverse events was statistically significantly lower for percutaneous closure in the non-randomised study of 381 patients (8% (15/195) compared with 23% (42/186) for surgical closure, p<0.001). [2]

Major adverse cardiovascular events were reported in 25% (64/259) of patients during a median follow up of 110 days in the retrospective UK and Irish registry of 259 patients.[5]

Stroke

In-hospital stroke

Stroke rates in hospital were not statistically significantly different between groups in the non-randomised study of 381 patients (1% (2/195) for percutaneous closure compared with 2% (4/186) for surgical closure, p=0.38). [2]

30-day stroke

30-day stroke rates were not statistically significantly different between patients having percutaneous closure and patients having surgical repair of PVLs in the

systematic review and meta-analysis of 2,373 patients (1.4% versus 3.3%, OR 1.94, 95% CI [0.95 to 3.96], p=0.069, I^2=0%). [1]

Embolic stroke within 30 days of the procedure was reported in 1% (2/200) of patients in the case series of 200 patients. [7]

Cerebrovascular accident was reported in 1 patient in the case series of 45 patients (no further details reported). [9]

Cardiac complications

Cardiac complications (complete atrioventricular block, air embolism, ventricular fibrillation) within 30 days of the procedure were reported in less than 1% (4/469) of patients in the retrospective Spanish registry of 469 patients. In the same study, emergency cardiac surgery within 30 days of the procedure was reported in 1% (6/469) of patients and pericardial effusion within 30 days of the procedure was reported in less than 1% (4/469) of patients. [4]

Tamponade

The rates of tamponade were not statistically significantly different between groups in the non-randomised study of 381 patients (less than 1% (1/195) for percutaneous closure compared with 2% (3/186) for surgical closure, p=0.58). [2]

Arrhythmia

Arrhythmia was reported in 2% (1/45) of patients who had percutaneous closure compared with 6% (2/35) of patients who had surgical closure within 5-year follow up in the non-randomised study of 87 patients (no statistically significant difference between groups, p=0.502).[3]

Arrythmia was reported in 4% (6/136) of patients during a mean follow up of 154 days in the retrospective registry of 136 patients; they all needed treatment. [6]

Cardiac resynchronisation therapy

Cardiac resynchronisation therapy was reported in1 patient during a mean follow up of 154 days in the retrospective registry of 136 patients. [6]

After load mismatch

After load mismatch was reported in 1 patient within a 2-year follow up in the case series of 45 patients. [9]

Renal failure

The rate of renal failure needing dialysis was statistically significantly lower for percutaneous closure in the non-randomised study of 381 patients (less than 1% (1/195) compared with 8% (14/186) for surgical closure, p<0.001). [2]

Acute renal insufficiency was reported in none of the patients who had percutaneous closure compared with 6% (4/63) of patients who had surgical repair after the procedure, in the non-randomised study of 131 patients.[8]

Acute kidney injury was reported in 11% (5/45) of patients in the case series of 45 patients (no further details reported). [9]

Prolonged ventilation

The rates of prolonged ventilation were not statistically significantly different between groups in the non-randomised study of 381 patients (0% (0/195) for percutaneous closure compared with 2% (3/186) for surgical closure, p=0.08). [2]

Pneumonia

The rate of pneumonia was statistically significantly lower for percutaneous closure in the non-randomised study of 381 patients (0% (0/195) compared with 9% (17/186) for surgical closure, p<0.001). [2]

Device embolisation

Device embolisation was reported in 2% (4/195) of patients having percutaneous closure in the non-randomised study of 381 patients. Three of the devices were snared percutaneously but 1 patient needed an open surgical intervention. [2]

Device embolisation within 30 days of the procedure was reported in 1% (6/469) of patients in the retrospective Spanish registry of 469 patients. All 6 device embolisations were successfully snared and retrieved. [4]

Late device embolisation was reported in 1 patient during a median follow up of 110 days in the retrospective UK and Irish registry of 259 patients.[5]

Device embolisation was reported in 3 patients in the retrospective registry of 136 patients: 1 was surgically resolved, 1 was percutaneously resolved and 1 was a late device embolisation. [6]

Device embolisation during the procedure was reported in 2% (4/200) of patients in the case series of 200 patients. The devices were retrieved percutaneously using either a snare or a bioptome. In the same study, device embolisation within 30 days of the procedure was reported in 1 patient; it was treated with an emergency cardiac surgery. [7]

Device embolisation was reported in 4% (2/45) of patients in the case series of 45 patients; 1 patient needed surgery for failed procedure. [9]

Device malposition

Device malposition was reported in 2% (1/46) of patients in the transcatheter group in the non-randomised study of 87 patients. [3]

Bleeding and other vascular complications

The rates of vascular complications in hospital were not statistically significantly different between groups in the non-randomised study of 381 patients (3% (6/195) for percutaneous closure compared with less than 1% (1/186) for surgical closure, p=0.14). In the same study, the rates of haemothorax or bronchial bleeding were not statistically significantly different between groups (2% (4/195) for percutaneous closure compared with 0% (0/186) for surgical closure, p=0.12). Three out of four patients had a haemothorax after a transapical access procedure. [2]

Haemothorax was reported in 4% (2/46) of patients in the transcatheter group and in 7% (3/41) of patients in the surgical group in the non-randomised study of 87 patients (no statistically significant difference between groups, p=0.663). The 2 patients from the transcatheter group had a transapical PVL closure. One was treated with drainage and the other had a thoracic re-exploration.
In the same study, the need for blood transfusions during the procedure was statistically significantly lower for percutaneous closure (65.21±158.07 ml) compared with surgical closure (1501.21 ml ± 958.15 ml, p<0.0001). Thirteen percent (6/46) of patients who had percutaneous closure had a blood transfusion compared with 100% (41/41) of patients who had surgical closure (p<0.0001). There was no blood loss for percutaneous closure compared with 1358.54 ml ± 969.01 ml for surgical closure (p<0.0001).
Bleeding or thrombosis events within 5-year follow up were reported in 4% (2/45) of patients who had percutaneous closure compared with none of patients who had surgical closure (no statistically significant difference between groups, p=0.502).[3]

Vascular complications and bleeding within 30 days of the procedure were reported in 9% (40/469) of patients in the retrospective Spanish registry of 469 patients.[4]

Bleeding was reported in 3% (4/136) of patients during a mean follow up of 154 days in the retrospective registry of 136 patients. [6]

Major bleeding within 30 days of the procedure was reported in 4% (8/200) of patients in the case series of 200 patients. Two patients had a vascular complication, 5 patients had a haemothorax and 1 patient had an intracranial haemorrhage. In the same study, coronary dissection was reported in 1 patient during the procedure. [7]

The need for blood transfusion during and after the procedure was statistically significantly smaller for percutaneous closure compared with surgical repair in the non-randomised study of 131 patients (16% [11/68] compared with 100% (63/63), p<0.001). None of the patients who had percutaneous closure had a haemorrhage after the procedure compared with 3% (2/63) of patients who had surgical repair. In the same study, haemothorax was reported in 1 patient who had percutaneous closure via the transapical approach compared with none of the patients who had surgical repair. The patient recovered before hospital discharge. [8]

Haemothorax was reported in 11% (5/45) of patients in the case series of 45 patients. [9]

Aortic perforation was reported in 1 patient during the procedure in a single case report of a patient who had percutaneous PVL closure. [10]

Haematoma of the groin was reported in 4% (2/46) of patients in the transcatheter group and in none of the patients in the surgical group in the non-randomised study of 87 patients (no statistically significant difference between groups, p=0.496). [3]

Haematoma within 30 days of the procedure was reported in 1% (6/469) of patients in the retrospective Spanish registry of 469 patients. [4]

Complication at femoral puncture site was reported in 1 patient during a mean follow up of 154 days in the retrospective registry of 136 patients. [6]

Pseudoaneurysm within 30 days of the procedure was reported in 3% (14/469) of patients in the retrospective Spanish registry of 469 patients. [4]

Femoral pseudoaneurysm was reported in 3% (2/68) of patients who had percutaneous closure compared with none of the patients who had surgical repair after the procedure, in the non-randomised study of 131 patients. The patients recovered before hospital discharge.[8]

Haemolysis

The rate of severe haemolysis aggravation was not statistically significantly different between groups in the non-randomised study of 87 patients (11% (5/46) for percutaneous closure compared with 0% for surgical closure, p=0.057). Four patients were prevented from further deteriorating by drug administration and blood transfusion; they recovered before hospital discharge. One patient died from haemolysis aggravation (also reported in the death section). In the same study, moderate haemolysis aggravation was reported in 1 patient in each group. Persistent severe haemolysis over a 5-year follow up was reported in 9% (4/45) of patients who had percutaneous closure and in none of patients who had surgical closure (no statistically significant difference between groups, p=0.127).[3]

New haemolysis needing transfusion was reported in 2% of patients during a median follow up of 110 days in the retrospective UK and Irish registry of 259 patients.[5]

New onset of haemolytic anaemia that was transient was reported in 1 patient during a mean follow up of 154 days in the retrospective registry of 136 patients; it was treated with blood transfusions. In the same study, recurrent haemolytic anaemia was reported in 2% (3/136) of patients. [6]

Haemolysis was reported in 6% (4/68) of patients who had percutaneous closure compared to none of the patients who had surgical repair after the procedure, in the non-randomised study of 131 patients. Two of these patients had acute renal insufficiency and needed continuous renal replacement therapy and blood transfusions. All patients recovered before discharge.[8]

Valve complications

Prosthetic impingement within 30 days of the procedure was reported in 3% (15/469) of patients in the retrospective Spanish registry of 469 patients. [4]

Valve surgery was reported in 6% of patients during a median follow up of 110 days in the retrospective UK and Irish registry of 259 patients; it included infective endocarditis and new valve leaflet interference in 1 patient each.[5]

Interference with prosthetic valve leaflets was reported in 1 patient during a mean follow up of 154 days in the retrospective registry of 136 patients. It was treated percutaneously. In the same study, valve surgery was reported in 2% (3/136) of patients. [6]

Prosthetic impingement within 30 days of the procedure was reported in 1 patient in the case series of 200 patients; the patient needed an emergency cardiac surgery. [7]

Infection

The severe infection or sepsis rate was statistically significantly lower for percutaneous closure in the non-randomised study of 87 patients (2% (1/46) compared with 20% (8/41) for surgical closure, p=0.011). [3]

Sepsis was reported in none of the patients who had percutaneous closure compared with 8% (5/63) of patients who had surgical repair after the procedure, in the non-randomised study of 131 patients.[8]

Infective endocarditis was reported in 1 patient in the case series of 45 patients. [9]

Anecdotal and theoretical adverse events

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

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve. The following databases were searched, covering the period from their start to 17 August 2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

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

Inclusion criteria for identification of relevant studies

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

List of studies included in the IP overview

This IP overview is based on 2,973 patients from 1 systematic review and meta-analysis, 3 retrospective non-randomised studies, 3 retrospective registries, 1 case series, 1 conference abstract and 1 single case report.[1-10]

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

Summary of key evidence on percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve

Study 1 Busu T (2018)

Study details

Study type	Systematic review and meta-analysis
Country	USA Studies included are from: Spain, Brazil, USA, Canada, Turkey, France, Poland, UK/Ireland, China, Switzerland, Korea and Italy.
Recruitment period	Literature search up until 20/10/2017
Study population and number	n=2,373 (1,511 percutaneous versus 862 surgical) patients with mitral or aortic PVL from 22 retrospective observational studies (5 comparative retrospective studies comparing the transcatheter approach versus the surgical approach and 17 single-arm retrospective studies)
Age and sex	Mean age range [50 to 70]; 66% male
Patient selection criteria	Not reported
Technique	Percutaneous closure or surgical repair
Follow up	Not reported
Conflict of interest/source of funding	None

Analysis

Study design issues:

- The review protocol was developed in accordance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines.

- The main outcomes of interest included (1) 30-day outcomes: procedural success defined as mild or less residual leak, stroke, hospital length of stay, and all-cause mortality, and (2) mid- and long-term outcomes: all-cause mortality at 1 year, symptomatic improvement, readmission for heart failure, and redo surgical intervention at maximum follow up.

- All noncomparative studies were pooled into a single study to generate comparisons of primary and secondary outcomes.

Study population issues:

- The primary indications for PVL intervention were congestive heart failure (66%), haemolytic anaemia (22%), and the mitral position was the most common PVL location (74%).

- There were statistically significant differences between the percutaneous and surgical groups for the following baseline characteristics: age (65.3 versus 60.3 years, p=0.001), female patients (31% versus 40%, p<0.001), haemolysis (19% versus 28%, p<0.001), both heart failure and haemolysis (33% versus 23%, p<0.001), bioprosthetic valve (47% versus 41%, p=0.011), mechanical valve (53% versus 59%, p=0.011) and aortic leak (27% versus 23%).

Other issues:

The following studies were included:
- Comparative studies: Angulo-Llanos (2016, n=51 P versus 36 S), Pinheiro (2016, n=10 P versus 25 S), Wells (2017, n=56 P versus 58 S), Alkhouli (2017, n=195 P versus 186 S) and Millan (2017, n=80 P versus 151 S).
- Case series: Goktekin (2016, n=21 P), Noble (2013, n=56 P), Bagate (2016, n=14 P), Smolka (2016, n=49 P), Garcia (2016, n=469 P), Calvert (2016, n=259 P), Aydin (2016, n=52 P), Jian (2016, n=13 P), Sanchez-Recalde (2014, n=20 P), Ruiz (2011, n=43 P), Alkhouli (2016, n=80 P), Cruz-Gonzalez (2014, n=33 P), Pate (2006, n=10 P), Genoni (2000, n=96 S), Choi (2013, n=52 S), Akins (2005, n=136 S) and Taramasso (2015, n=122 S).

Key efficacy findings

Number of patients analysed: 2,373 (1,511 percutaneous versus 862 surgical)

Clinical outcome	**Comparison surgical versus percutaneous treatment**	**p value**	**I^2**
Technical success	Percutaneous closure was associated with lower rates of technical success: 96.7% vs 72.1%, OR 9.7, 95% CI [5.48 to 17.08]	**<0.001**	67.8%
Length of stay	Percutaneous closure was associated with shorter hospital stay standardised difference in mean –0.832, 95% CI [–0.976 to –0.689]	**<0.001**	53.9%
Readmission for heart failure	Similar readmission rates for heart failure between the surgical and percutaneous groups: 13.0% vs 26.4%, OR 0.51, 95% CI [0.15 to 1.77]	0.29	81.1%
Improvement in NYHA heart failure classification	Similar improvement in NYHA heart failure classification between the surgical and percutaneous groups: 67.4% vs 56%, OR 1.37, 95% CI [0.21 to 8.94]	0.74	91.5%

Reoperation	Similar reoperation rates between the surgical and percutaneous groups: 9.1% vs 9.9%, OR 0.72, 95% CI [0.49 to 1.06]	0.1	36.1%

Key safety findings

Clinical outcome	**Comparison surgical versus percutaneous treatment**	**p value**	**I^2**
30-day mortality	Percutaneous closure was associated with lower rates of 30-day mortality: 8.6% vs 6.8%, OR 1.90, 95% CI [1.33 to 2.73]	<0.001	0%
30-day stroke	Percutaneous closure was associated with lower rates of 30-day stroke (trend): 3.3% vs 1.4%, OR 1.94, 95% CI [0.95 to 3.96]	0.069	0%
1-year mortality	Similar mortality rates at 1 year between the surgical and percutaneous groups: 17.3% vs 17.2%, OR 1.07, 95% CI [0.79 to 1.44]	0.67	0%

Study 2 Alkhouli M (2017)

Study details

Study type	Retrospective comparative study
Country	USA (single centre)
Recruitment period	1995 to 2015
Study population and number	n=381 (195 percutaneous versus 186 surgical) patients with mitral paravalvular leak
Age and sex	Mean 66 years; 55% (209/381) male
Patient selection criteria	Patients who had treatment of mitral PVL during the study period. The indications for percutaneous repair were severe dyspnoea with moderate or severe PVL and clinically significant haemolytic anaemia. All patients who were treated before January 2006 were referred for surgical intervention. After January 2006, criteria to refer patients for redo operation at the outset were: active endocarditis; a very large leak involving more than one-half of the circumference of the sewing ring; rocking motion or instability of the prosthesis; and need for concomitant surgical intervention. Patients who did not meet 1 of these criteria and those deemed at very high risk for reoperation were referred for percutaneous closure.
Technique	Percutaneous technique: the antegrade transseptal approach was used to cannulate the PVLs in most of the patients. The following devices were used: the Amplatzer Vascular Plug II (AVP-II, St. Jude Medical, St. Paul, Minnesota [71%]), the Amplatzer Duct Occluder (7%),the Amplatzer Septal Occluder (5%), and the Amplatzer Muscular VSD Occluder or combinations (9%). There was a mean of 1.6 devices placed. Surgical technique: use of a patch (2%), two-layer suture repair (8%) or single-layer pledgeted suture repair (40%). When repair was not possible, re-replacement of the mitral valve with a biological or a mechanical prosthesis was done (50% of surgical closures).
Follow up	Mean 4 years
Conflict of interest/source of funding	None

Analysis

Follow-up issues:
- In-hospital data were available for all patients, and long-term mortality data were available for 98.2% of patients.
- There was a statistically significant difference between the lengths of follow up available for the percutaneous (3.7 ± 2.7 years) and the surgical (7.4 ± 5.7 years) groups (p<0.001).

Study design issues:

IP overview: Percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve

- The primary efficacy endpoint was technical success.
- The primary safety endpoint was freedom from in-hospital death and major adverse events.
- Secondary endpoints were reintervention rates over time and long-term freedom from death in patients who had surgical treatment compared with those who had surgical treatment after a failed percutaneous treatment attempt.

Study population issues:

There were statistically significant differences between the percutaneous and surgical groups for the following baseline characteristics: age (67.5 years versus 63.8 years, p=0.003), heart failure NYHA class 3 or 4 symptoms (77.9% versus 66.7%, p=0.01), time from surgery to repair (57.0 months versus 115.6 months, p<0.001), number of sternotomies (1.9 versus 2.7, p<0.001), atrial fibrillation/ flutter (72.3% versus 60.2%, p=0.02), chronic renal insufficiency (31.8% versus 43.0%, p=0.02), active endocarditis (0% versus 3.8%, p=0.006), rheumatic heart disease (24.1% versus 51.1%, p<0.001), prior chest radiation (7.2% versus 1.1%, p=0.003), prior permanent pacemaker (34.9% versus 12.9%, p<0.001), number of mitral PVLs (1.3 versus 1.5, p=0.008), number of PVLs ≤ 2 (95.4% versus 87.1%, p=0.004), location of the leak (p<0.001) and left ventricular ejection fraction (61.0% versus 57.0%, p=0.006).

Other issues: This study was included in the systematic review and meta-analysis by Busu et al. (2018).

Key efficacy findings

- Number of patients analysed: 381 (195 percutaneous versus 186 surgical) patients with mitral paravalvular leak
- Technical success rate (defined as absence of procedural mortality or stroke; successful access, delivery, and retrieval of the device delivery system; proper placement and positioning device(s); freedom from unplanned surgical or interventional procedures related to the device or access procedure; continued intended safety and performance of the device, including no evidence of structural or functional failure of the prosthetic valve; no specific device-related technical failure issues and complications; and reduction of regurgitation to no greater than mild (1+) paravalvular regurgitation [and without associated haemolysis]): 70.1% versus 95.5%, p<0.001.
- There were no statistically significant predictors of technical failure in patients who had percutaneous PVL repair.
- The need for subsequent surgical treatment statistically significantly decreased with increasing experience with percutaneous PVL closure (p<0.001).

In-hospital and long-term outcomes

Clinical outcome	All patients	Percutaneous PVL closure	Surgical PVL closure	p value
Residual leak				**<0.001**
None	54% (206/381)	40% (78/195)	83% (128/186)	
Mild (grade I)	20.5% (78/381)	30% (58/195)	13% (20/186)	

Moderate (grade II)	11% (41/381)	19% (36/195)	3% (5/186)	
Severe (grade III)	6% (24/381)	11% (22/195)	1% (2/186)	
Hospital length of stay (days, mean±SD)	9.1±10.2	5.3 ± 7.6	14.0 ± 11.0	**<0.001**
Reintervention	14% (54/381)	11% (22/195)	17% (32/186)	0.10
Reoperation	10% (38*/381)	10% (20/195)	10% (19/186)	0.88
Repeat percutaneous intervention	6% (22/381)	3% (5/195)	9% (17/186)	**0.006**
Time to reintervention (month)	28.2 ± 38.6	6.2 ± 7.4	42.8 ± 43.8	**<0.001**

*As written in the journal article.

Key safety findings

In-hospital and long-term outcomes

Clinical outcome	All patients	Percutaneous PVL closure	Surgical PVL closure	p value
In-hospital death	6% (22/381)	3% (6/195)	9% (16/186)	**0.027**
In-hospital major adverse events	15% (57/381)	8% (15/195)	23% (42/186)	**<0.001**
Stroke	2% (6/381)	1% (2/195)	2% (4/186)	0.38
Vascular complications	2% (7/381)	3% (6/195)	<1% (1/186)	0.14
Renal failure requiring dialysis	4% (15/381)	<1% (1/195)	8% (14/186)	**<0.001**
Prolonged ventilation	<1% (3/381)	0% (0/195)	2% (3/186)	0.08
Pneumoniae	4% (17/381)	0% (0/195)	9% (17/186)	**<0.001**
Tamponade	1% (4/381)	<1% (1/195)	2% (3/186)	0.58
Haemothorax/bronchial bleeding*	1% (4/381)	2% (4/195)	0% (0/186)	0.12
Embolization needing surgery†	<1% (1/381)	<1% (1/195)	-	-
Overall mortality	59% (225/381)	50% (98/195)	68% (127/186)	**<0.001**

*Three patients had haemothorax after transapical access.
†Four patients in total had device embolization; 3 were snared percutaneously and 1 needed open surgical intervention.

In a multivariate logistic regression analysis, only active endocarditis (p=0.001), chronic renal failure (p=0.002), and severe mitral annular calcifications (p=0.02) were statistically significant predictors of in-hospital mortality in the overall cohort.

After risk adjustment, there was no statistically significant difference in long-term survival between patients who had percutaneous compared to surgical treatment of PVLs (p=0.16

Study 3 Zhang Y (2019)

Study details

Study type	Retrospective comparative study
Country	China
Recruitment period	2009 to 2015
Study population and number	n=87 (46 percutaneous versus 41 surgical) consecutive patients with PVL
Age and sex	Mean 55 years; 60% (52/87) male
Patient selection criteria	Indications for PVL closure: (1) severe symptoms of dyspnoea or clinically significant haemolytic anaemia and (2) moderately severe or severe paravalvular prosthetic regurgitation. Exclusion criteria for transcatheter therapy: prosthetic dysfunction; the leak is so large that prosthetic becomes unstable; acute active endocarditis; intracardiac thrombi or vegetation and associated with other heart disease requiring surgical treatment. Exclusion criteria for surgical repair: any contraindications for open surgery or life expectancy of less than 1 year.
Technique	Transcatheter repair: for aortic PVL, femoral artery access with a retrograde approach was used. For mitral PVL, the anterograde approach was used except for challenging mitral PVLs where transapical closure was preferred. For patients with mitral and aortic mechanical PVL, multiple techniques were needed for the closure of the mitral PVL. Occluding devices: mVSD, PDA, Plug II, and DO II (STARWAY Medical Technology Co., Ltd., Beijing, China). Surgical repair: the approach was from the left atrial side for mitral PVLs. An ascending aorta incision was used to expose the aortic PVLs.
Follow up	Mean 4 years [range 1 to 84 months]
Conflict of interest/source of funding	No conflict of interest. The study was supported by a research fund for the scientific and technical project of shanghai municipality and a research fund for the scientific and technical project of shanghai chest hospital.

Analysis

Follow-up issues:

- Most patients were contacted by message, telephone, or outpatient review to determine their symptoms and vital status every 6 to 12 months. The living status of the patients lost to follow up was indirectly verified by the local neighbourhood committee.

- All patients in both groups except 2 surgical patients completed the follow up.

Study design issues:
Study population issues:

- The patients (6%) who had the procedure with an active endocarditis or for whom the main data was missing have been excluded prospectively.
- In the 46 patients who had percutaneous treatment, 20 had an aortic PVL, 23 had a mitral PVL and 3 had both.
- In the 41 patients who had surgical treatment, 10 had an aortic PVL, 30 had a mitral PVL and 1 had both.
- There was a statistically significant difference between groups for the mitral PVL (p=0.027).
- 6 patients had transapical PVL closure (the 4 latter ones had a minimal incision). 6 patients had a 2-step procedure.

Key efficacy findings

Number of patients analysed: 87 (46 percutaneous versus 41 surgical)

Procedural details

Clinical outcome	Transcatheter group	Surgery group	p value
Blood transfusion (ml)	65.21±158.07	1501.21±958.15	**<0.0001**
Patients who received transfusion	13% (6/46)	100% (41/41)	**<0.0001**
Blood loss (ml)	0	1358.54±969.01	**<0.0001**
Procedural duration (min)	107.15±60.66	345.85±100.76	**<0.0001**
Hospital stay after intervention (days)	12.42±13.20	29.57±24.65	**0.003**

In-hospital outcomes

Clinical outcome	Transcatheter group	Surgery group	p value
Procedural success*	82.60%	90.24%	0.303

*Same definition as in study 2.

There were 8 failed procedures in the transcatheter group: 2 cases of an inability to cross the guidewire or delivery sheath; 1 prosthetic leaflet impingement handled by withdrawing the occluder and converting to surgical therapy; 4 patients still had significant residual PVL after the devices were deployed; and 1 patient died from haemolysis.

5-year follow-up outcomes

Clinical outcome	Transcatheter group	Surgery group	p value
Overall survival	74.4%	72.0%	0.451
Cardiac-related survival	84.1%	74.7%	0.192
Clinical success**	69.50%	73.00%	0.711

**Defined as an improvement of at least one NYHA functional class with no rehospitalisation or reinterventions for the index reason.

Key safety findings

Major adverse events[a]

Clinical outcome	Transcatheter group	Surgery group	p value
Death	2% (1/46)*	15% (6/41)	**0.048**
Severe infection/Sepsis	2% (1/46)	20% (8/41)	**0.011**
Low cardiac output syndrome	0	12% (5/41)	**0.020**
Serious haemolysis aggravation	11% (5/46)**	0	0.057
Emergency surgery	0	2% (1/41)	0.471
Thoracic re-exploration	2% (1/46)	5% (2/41)	0.599
Complete atrioventricular block	0	2% (1/41)	0.471
Total[a]	17% (8/46)	56% (23/41)	**<0.0001**

[a]The adverse events were counted in case-time manner. Multiple mentions were possible.

*The patient died from acute renal insufficiency secondary to acute haemolysis 6 days after the procedure.
**4 patients were prevented from further deteriorating by drug administration and blood transfusion; they recovered before hospital discharge. One patient died from haemolysis aggravation (also reported in the death section).

Minor adverse events[a]

Clinical outcome	Transcatheter group	Surgery group	p value
Haemothorax	4% (2/46)[c]	7% (3/41)	0.663
Haematoma of the groin	4% (2/46)	0	0.496
Device malposition[d]	2% (1/46)	0	1
Moderate haemolysis aggravation	2% (1/46)	2% (1/41)	1
Transient malignant arrhythmia	0	2% (1/41)	0.471
Residual obvious PVL at discharge[b]	15% (7/46)	2% (1/41)	0.061
Total[a]	28% (13/46)	15% (6/41)	0.125

[a] The adverse events were counted in case-time manner. Multiple mentions were possible.
[b] The residual obvious PVLs in transcatheter group include unable to cross the defect (n=2), prosthetic impingement (n=1), significant residual PVL after devices deployed (n=4).
[c] These 2 patients had a transapical PVL closure. One was treated with drainage and the other had a thoracic re-exploration.
[d] The device was snared out and a suitable device was redeployed.

5-year follow-up outcomes

Clinical outcome	Transcatheter group (n=45)	Surgery group (n=35)	p value
Death	18% (8/45)*	14% (5/35)	0.675
Cardiac-related death	9% (4/45)	6% (2/35)	0.691
Non-cardiac death	9% (4/45)	3% (1/35)	0.379
Unknown	0	6% (2/35)	0.188
Bleeding/thrombosis events	4% (2/45)	0	0.502
Arrhythmia needing pacemaker	2% (1/45)	6% (2/35)	0.578
Re-hospitalisation	11% (5/45)	14% (5/35)	0.670
Releak	4% (2/45)	9% (3/35)	0.649
Persistent severe haemolysis	9% (4/45)	0	0.127

*Four patients died from severe post-procedure haemolysis within 1 year of hospital discharge. Four patients died from non-cardiac causes (2 from severe pneumonia, 1 from suicide, and 1 from warfarin-related lower intestinal haematorrhea).

Logistic regression analysis showed that mVSD occluder was an independent predictor of post-procedure haemolysis aggravation (OR 11.66, 95% CI 1.23 to 110.80, p=0.012) and the difference remained statistically significant after multivariate adjustment. Baseline haemolysis and other devices (PDA, Plug II, and DO II) are unrelated to post-procedure haemolysis aggravation in this group.

Study 4 Garcia E (2017)

Study details

Study type	Retrospective registry
Country	Spain (19 centres)
Recruitment period	2002-14
Study population and number	n=469 (514 first attempt PVL closure) patients with PVL
Age and sex	Mean 68 years; 53% male
Patient selection criteria	Patients with symptomatic heart failure or clinically significant symptomatic haemolytic anaemia; moderately severe or severe paravalvular prosthetic regurgitation and absence of active endocarditis. All the procedures were to treat surgical valves.
Technique	Percutaneous PVL closure with the following devices: AVP III, AVP III+ ductal occluder, AVP III+other, ductal occluder, ventricular septal occluder and other.
Follow up	30 days
Conflict of interest/source of funding	Four of the authors are proctors for St.Jude Medical. One of the authors was partially supported by the 'Programa de intensificacion' for researchers of Gerencia Regional de Salud.

Analysis

Follow-up issues: Long-term clinical and echocardiographic follow up was not available for all patients.
Study design issues:
- The collected variables included: demographics, baseline characteristics, clinical indications por PVL closure, procedural characteristics and periprocedural adverse events occurring within 30 days of the procedure.
- Centres had different volumes of procedures.
- The choice for a PVL closure versus re-do surgery was left at the physicians' discretion and may have varied over time.
- The clinical and echocardiographic results were self-reported and there was no independent adjudication.

Study population issues:
- The main indications for the procedure were heart failure (39% of patients) and haemolytic anaemia (9%).
- The mean logistic EuroSCORE was 17.52±11.56%.
- The mean time since last valve replacement to PVL attempt was 8.53±7.82 years.
- Treated defects were mostly paramitral (70%) and involved mechanical prostheses (89% mitral prostheses, 78% aortic prostheses).
- Transfemoral access was used in 94% of patients and the antegrade transseptal approach in 45% of patients.

Other issues: This study was included in the systematic review and meta-analysis by Busu et al. (2018).

Key efficacy findings

Number of patients analysed: 469

- Multiple devices were used in single defects in 15% of patients.

Success rates

	Overall	Mitral valves	Aortic valves	p value (comparison mitral vs aortic)
Technical success Successful delivery of a PVL closure device without interference with the valve prosthesis.	86.6%	84.8%	90.8%	0.064
Procedural success Technical success and 1 or more than 1 grade regurgitation reduction.	73.2%	70.6%	74.2%	0.393

Multivariate analysis:
- The independent predictors for procedural success in mitral lesions were the type of device used (Amplatzer AVP III versus others, HR 2.68 [1.29 to 5.54], p=0.008) and the number of procedures done at the centre (top quartile versus others, HR 1.93 [1.051 to 3.53], p=0.03).
- The only independent predictor for procedural success in aortic leaks was the leak size (≥10 mm versus <10 mm, HR 3.077 [1.13 to 8.33], p=0.027).

Key safety findings

Periprocedural and adverse events at 30 days

Event	% of patients (n=469)
No complications	80.2%
Vascular complications and bleeding	8.6%
Pseudoaneurysm	2.9% (14/469)
Haematoma	1.2% (6/469)
Cardiac (complete atrioventricular block, air embolism, ventricular fibrillation)	0.8%
Pericardial effusion	0.8%
Device embolisation*	1.2% (6/469)
Emergency cardiac surgery	1.2% (6/469)
Prosthetic impingement	3.1% (15/469)
All-cause death	4.5%
All-cause death, stroke or emergency surgery	5.6%

*All 6 device embolisations were successfully snared and retrieved.

Multivariate analysis:

- The only independent predictor for combined major adverse events was NYHA functional Class 4 (HR 4.2 [1.42 to 12.34], p=0.009).
- The only independent predictor for all-cause mortality at 30 days was NYHA functional Class 4 (HR 6.32 [1.94 to 20.8], p=0.002).

Study 5 Calvert P (2016)

Study details

Study type	Retrospective registry
Country	UK and Ireland (20 centres)
Recruitment period	2004-15
Study population and number	n=259 patients (308 PVL closures) with PVL
Age and sex	Mean 67 years; 72% (186/259) male
Patient selection criteria	Patients with PVL. PVLs were often multiple and had complex morphology.
Technique	Most percutaneous device closures were done under general anaesthesia with transoesophageal echocardiography guidance. Mitral valve PVLs were generally closed via a transvenous route with transseptal puncture in the anterograde direction. Some operators preferred to cross mitral PVLs in a retrograde direction either via transapical access or via femoral artery access through the aortic valve, especially for PVLs close to the atrial septum. Aortic valve PVLs were generally crossed in a retrograde direction with either femoral or radial arterial access. Devices to close PVLs were selected by physician preference: AVP3 (62.5% of procedures), mVSD (15%), AVP2 (7%), AVP4 (6%), PLD (4%) and ADO (3%).
Follow up	Median follow up of 110 (7 to 452) days
Conflict of interest/source of funding	Dr Calvert has received funding from the Academy of Medical Sciences. Dr Daniels is supported by the Welcome Trust. Seven of the authors proctor for St Jude Medical. St Jude Medical has covered travel, registration, and accommodation expenses for Dr Calvert to attend international cardiology congresses.

Analysis

Follow-up issues:
Study design issues: Where analysis pertained to patient-related outcomes, only final attempts at percutaneous PVL closure were included in the analysis.

Study population issues:

- The main indications for closure were heart failure (80%) and haemolysis (16%).
- The procedure was elective (81%), urgent (17%) or emergent (2%).
- The median time from last valve surgery to percutaneous closure attempt was 4.7 years (range 1.4 to 8.9), and 28% of patients had had more than 1 previous valve surgery (also reported as 27% in same paper).
- The target valve was the aortic valve in 48% of patients, the mitral valve in 44%, both valves in 2% but also the pulmonic valve in 1 patient. One patient had a PVL of a mitral annuloplasty ring treated percutaneously.

Transcatheter valves accounted for 5% of PVLs treated. The majority of PVLs were around mechanical valves (61.5%).
- Preprocedural leak was severe (61%), moderate (34%), or mild (5.7%) and was multiple in 37%.

Other issues: This study was included in the systematic review and meta-analysis by Busu et al. (2018).

Key efficacy findings

Number of patients analysed: 259

- Devices were successfully implanted in 91% of patients, via radial (7%), femoral arterial (52%), femoral venous (33%), and apical (7%) approaches.

- More than 1 closure procedure was needed in 19% of patients.

Reduction in severity of paravalvular leak

Severity of paravalvular leak	Before surgery	After surgery
Severe	61.0%	6.7%
Moderate	34.0%	18.6%
Mild	5.7%	41.3%
None	0%	33.3%

PVL improved statistically significantly following closure ($p<0.001$).

Improvement in NYHA heart failure classification

NYHA classification	Before surgery	After surgery
4	15.3%	3.2%
3	51.6%	7.6%
2	26.2%	39.5%
1	6.9%	49.7%

The mean NYHA class statistically significantly improved from 2.7±0.8 before the procedure to 1.6±0.8 over a median follow up of 110 days (range 7 to 452) ($p<0.001$).

Key safety findings

Hospital mortality

Type of procedure	Hospital mortality rate
Overall	3.9%
Elective	2.9%
In-hospital urgent	6.8%
Emergency	50%

There was a statistically significant difference in the hospital mortality rate between the types of procedures (p<0.001, log rank).

Major adverse cardiovascular events (MACE) during follow up

MACE	% of patients
All	24.8% (64/259)
Death	16%
Valve surgery*	6%
Late device embolisation	<1% (1/259)
New haemolysis requiring transfusion	1.6%

*Infective endocarditis and new valve leaflet interference happened in 1 patient each.

- Mitral PVL was associated with higher MACE (hazard ratio [HR], 1.83 [1.15 to 2.91]; p=0.011) and trend toward death (HR, 1.63 [0.99 to 2.69]; p=0.055). Mechanical valves were not associated with MACE (HR, 1.17 [0.68 to 2.00]; p=0.57) or death (HR, 0.65 [0.39 to 1.09]; p=0.10).

- Factors independently associated with death were the degree of persisting leak (HR, 2.87 [1.07 to 7.73]; p=0.037), New York Heart Association class (HR, 2.00 [1.14 to 3.50]; p=0.015) at follow up and baseline creatinine (HR, 8.19 [2.39 to 28.08]; p=0.001).

- The only factor independently associated with MACE was the degree of persisting leak at follow up (HR, 3.01 [1.48 to 6.12]; p=0.002).

Study 6 Onorato E M (2020)

Study details

Study type	Retrospective registry
Country	9 countries (Italy, Poland, Lithuania, France, Hungary, Kazakhstan, Cyprus, Morocco and Romania; 21 centres)
Recruitment period	2014-18
Study population and number	n=136 consecutive patients (179 devices) with PVL from mitral or aortic valves
Age and sex	Mean 66 years; 58% (male)
Patient selection criteria	Patients with a moderate-to-severe PVL causing heart failure or haemolysis with the need for recurrent blood transfusions who were considered high risk for surgery
Technique	Two- and three-dimensional TEE was used throughout each procedure. Procedures were done under general anaesthesia or conscious sedation. In a subset of patients, transapical catheter based mitral PVL closure procedures were performed with a fusion of real-time 3D TEE and cardiac fluoroscopy imaging. The Occlutech PLD device was used.
Follow up	Mean 154 days.
Conflict of interest/source of funding	The main author is a consultant for Occlutech. The other authors have no conflicts of interest to declare.

Analysis

Follow-up issues: Safety data were collected from 136 patients. Baseline and 6-month follow-up data from 106 patients (69 mitral and 37 aortic) were considered in the analyses, if not mentioned otherwise.

Study design issues: There was no evaluation of TEE by a central core laboratory, nor was an audit of the records performed.

Study population issues:
- Main indications were heart failure (49.3%), haemolytic anaemia (4.8%), or both (43%).
- Twenty-five (36.8%) of the mitral valve leak and 3 (8.3%) of the aortic valve leak patients were dependent on blood transfusions.
- More than 80% of PVL had a maximum diameter of less than 10 mm and either a crescent or oval shape.

Key efficacy findings

Number of patients analysed: 106

- Most ML and AL were closed with one PLD per leak (79.4% and 75.6%, respectively).

IP overview: Percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve

- Median procedural time for ML closure was 122.5 minutes (range 110 to 135 minutes) in transapical cases and 62.5 minutes (range 48 to 125 minutes) in transseptal cases.

Success rates

Device success at day of implantation (n=136) Patients with stable implantation and paravalvular regurgitation reduced to small or less.	88.9% [95% CI 80.0% to 94.3%]
Procedural success at day of implantation (n=136) Device success and no procedure- or device-related major complication.	86.6% [95% CI 77.4% to 92.5%]
Clinical success at 6 months Patients in NYHA Class 1 or 2 or patients no longer dependent on blood transfusions at 6 months, who did not experience procedure- or device-related major complications.	86.5% [95% CI 78.5% to 91.9%]

Reduction in severity of paravalvular leak

	Mitral valve (% of patients) n=69		**Aortic valve (% of patients) n=37**	
Severity of paravalvular leak	**Before surgery**	**6 months after surgery**	**Before surgery**	**6 months after surgery**
Severe	97.1%	4.5%	91.9%	2.7%
Moderate	1.4%	7.6%	8.1%	10.8%
Small	1.4%	56.1%	0%	81.1%
None	0%	31.8%	0%	5.4%

PVL improved statistically significantly following closure ($p<0.0001$) for both mitral and aortic PVLs.

One patient underwent repeat closure 4 months after the index procedure for significant residual leak.

Improvement in NYHA heart failure classification

	Mitral valve (% of patients) n=69		**Aortic valve (% of patients) n=37**	
NYHA classification	**Before surgery**	**6 months after surgery**	**Before surgery**	**6 months after surgery**
4	25%	4.3%	11.1%	2.8%
3	61.8%	11.6%	52.8%	0%
2	11.8%	53.6%	33.3%	33.3%
1	1.5%	30.4%	2.8%	63.9%

NYHA classification improved statistically significantly following closure ($p<0.0001$) for both mitral and aortic PVLs.

The proportion of patients with NYHA Class 3/4 decreased from 77.3% at baseline to 16.9% at latest follow up (also reported as ''the proportion of patients in NYHA Class 3/4 decreased from 86.8% at baseline to 11.4% at follow up'' in the same paper).

Improvement of haemolytic anaemia

	Mitral valve n=69		**Aortic valve n=37**	
	Before surgery	**6 months after surgery**	**Before surgery**	**6 months after surgery**
% of patients in need of haemolysis-related blood transfusion	36.8%	5.9%	8.3%	0%

Key safety findings

Complications

	Mitral valve n=92	**Aortic valve n=44**
Device embolisation (surgically resolved)	1% (1)	0%
Device embolisation (percutaneously resolved)	1% (1)	0%
Late device embolisation	1% (1)	0%
Interference with prosthetic valve leaflets (percutaneously resolved)	1% (1)	0%
New-onset haemolytic anaemia requiring transfusions (transient)	1% (1)	0%
Complication at femoral puncture site	1% (1)	0%
Need for repeat procedure	1% (1)	0%
Arrhythmias requiring treatment	5% (5)	2% (1)
Bleeding complication	3% (3)	2% (1)
Recurrent haemolytic anaemia	3% (3)	0%
Valve surgeries	2% (2)	2% (1)
Cardiac resynchronisation therapy	1% (1)	0%
Death following surgical valve replacement	1% (1)	0%
Sudden unexplained death	1% (1)	0%
Stroke death (1 haemorrhagic, 1 ischaemic)	2% (2)	0%
Death (disease-related)	4% (4)	5% (2)
All-cause mortality	9% (8)	5% (2)
All-cause mortality (mitral +aortic)	7.4% (10)	

Study 7 Sorajja P (2014)

Study details

Study type	Retrospective case series
Country	USA (single centre)
Recruitment period	2004 to 2013
Study population and number	n=200 consecutive patients with paravalvular prosthetic regurgitation
Age and sex	Mean 66 years; 58% (115/200) male
Patient selection criteria	Inclusion criteria: severe symptoms of dyspnoea or clinically significant haemolytic anaemia; moderately severe or severe paravalvular prosthetic regurgitation; absence of active endocarditis; regurgitation involving one-third or less of the circumference of the prosthetic annulus and absence of an unstable or rocking prosthesis; and informed consent. Echocardiography was the primary imaging modality for assessment. The Amplatzer occluder device was used.
Technique	Percutaneous PVL repair
Follow up	30 days
Conflict of interest/source of funding	The authors reported that they had no relationships relevant to the contents of this paper to disclose.

Analysis

Follow-up issues:
-Of the patients who had percutaneous repair, 3 declined use of their medical record for research. The remaining 200 patients form the cohort for analysis.
- Patients were contacted by telephone, mailed questionnaire, and clinical visit to determine vital status and adverse events within 30 days of the procedure.

Study design issues:
-This study sought to assess the learning curve for percutaneous repair of paravalvular prosthetic regurgitation.
- Patients were stratified into 4 groups by sequence for analysis: group 1, cases 1 to 49; group 2, cases 50 to 99; group 3, cases 100 to 149; and group 4, cases 150 or later.

Study population issues:
-A total of 243 paravalvular defects (74% mitral; 26% aortic) were treated.
- Heart failure was the predominant clinical indication for the procedure (94%) and haemolytic anaemia (31%) came second.
-53% (106/200) of patients had already had 2 sternotomies or more.
- The STS estimated operative mortality was 6.3 ± 5% (range 0.9% to 33.7%).
-Among the 4 groups, there was a nonsignificant trend for higher surgical risk in earlier patients (p= 0.06 for STS risk score).

Key efficacy findings

Number of patients analysed: 200

Procedural outcomes

Successful deployment of the device	92% (184/200)
Mean overall procedure time	138 ± 48 minutes
Procedural success Reasons for procedural failure included: 8 prosthetic leaflet impingements*, 6 devices deployed with residual severe regurgitation, 5 device embolisations, 3 inability to cross with guidewire, 2 inability to cross with delivery sheath and 1 coronary dissection.	89% (178/200)

* 1 patient with prosthetic leaflet impingement needed emergent cardiac surgery.

Learning curve

- Compared with the other groups, there was a greater use of left ventricular apical puncture for creation of an arteriovenous rail for patients in group 1 (22% vs. 0 to 6% in other groups; chisquare =18.7; p = 0.0003). Sequential device and anchor wire techniques were also used almost exclusively for those in the latter 2 groups (group 3, 48%; group 4, 43%) compared with earlier patients (group 1, 0%; group 2, 4%; chisquare = 49.4; p < 0.0001).
- Procedure order was inversely related to procedure time (p < 0.0001), contrast volume administered (p = 0.01), fluoroscopy time (p =0.08), and length-of-hospital stay (p = 0.007). These changes plateaued soon after increased use of 3-dimensional echocardiography and more operator experience with special catheter techniques, with no significant improvements being present in groups 3 and 4.
- There were no differences in the achievement of device deployment (range for 4 groups, 86% to 94%) or acute procedure success over the course of the clinical experience.

Key safety findings

Procedural and 30-day events

		Quartile			
	Total	**1st**	**2nd**	**3rd**	**4th**
Intraprocedural device embolisation	2% (4/200)***	2% (1/50)	4% (2/50)	0%	2% (1/50)
Major bleeding	4% (8/200)	10% (5/50)	4% (2/50)	0%	2% (1/50)
Vascular complication	1% (2/200)	2% (1/50)	2% (1/50)	0%	0%
Haemothorax	2.5% (5/200)	8% (4/50)	0%	0%	2% (1/50)
Intracranial haemorrhage	<1% (1/200)	0%	2% (1/50)	0%	0%
Embolic stroke	1% (2/200)	2% (1/50)	2% (1/50)	0%	0%
Emergency cardiac surgery	1% (2/200)	0%	2% (1/50)	2% (1/50)	0%
For prosthetic impingement	<1% (1/200)	0%	2% (1/50)	0%	0%
For device embolisation	<1% (1/200)	0%	0%	2% (1/50)	0%
Coronary dissection	<1% (1/200)	0%	0%	0%	2% (1/50)
Elective cardiac surgery for unsuccessful repair*	1.6% (3/200)	2% (1/50)	6% (3/50)	0%	0%
Death	2% (4/200)	4% (2/50)	2% (1/50)	2% (1/50)	0%
Sudden death	<1% (1/200)	2% (1/50)	0%	0%	0%
Cardiac tamponade	<1% (1/200)	0%	0%	2% (1/50)	0%
Sepsis	1% (2/200)	2% (1/50)	2% (1/50)	0%	0%
Death, stroke, or emergency surgery	4% (8/200)	6% (3/50)	6% (3/50)	4% (2/50)	0%
Death, stroke, major bleeding, or emergency surgery	8% (16/200) **	16% (8/50)	10% (5/50)	4% (2/50)	2% (1/50)

*The 3 patients who had elective cardiac surgery each had an uncomplicated, unsuccessful attempt at percutaneous repair before surgery.
**Numbers corrected by the analyst.
***The devices were retrieved percutaneously using either a snare or a bioptome.

Study 8 Yang C (2020)

Study details

Study type	Retrospective comparative study
Country	China (3 centres)

IP overview: Percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve

Recruitment period	2000 to 2016
Study population and number	n=131 (68 percutaneous PVL closure versus 63 surgical repair)
Age and sex	68% (89/131) male Age range: [27 to 73] years
Patient selection criteria	Patients in both groups were clinically evaluated to have surgical or percutaneous correction of paravalvular prosthetic regurgitation because more than moderate PVL regurgitation induced congestive heart failure or haemolysis. Patients with a PVL were referred for transcatheter closure if they met the following criteria: severe symptoms of dyspnoea or clinically significant haemolytic anaemia, moderately severe or severe paravalvular prosthetic regurgitation, and the absence of active endocarditis. The 2 groups of patients were not treated in the same period. Since the centres started using transcatheter closure in 2010, 68 patients had transcatheter closure of a PVL after June 2010. To make both groups comparable and to do a propensity score matching analysis, patients with a large PVL that the surgeons determined was unsuitable for percutaneous closure were excluded from the study.
Technique	Surgical treatment group: surgical repair of PVL or valve re-replacement. Transcatheter closure group: different types of Amplatzer occluder (AGA Medical Corp., Plymouth, Minnesota, United States) devices were used off-label. Multiple devices were used when there was a residual shunt. For mitral PVLs, when it was difficult to advance the catheter through the PVL, a transseptal puncture was done. For patients who had previously had combined mitral and aortic valve replacement with a mechanical valve, the closure of a mitral PVL retrogradely via the femoral artery was difficult. Therefore, the mitral PVL was approached retrogradely via a transapical access. In this subgroup, a left mini-thoracotomy was done with apical cardiac exposure under general anaesthesia.
Follow up	Transcatheter group: median 28 months Surgical group: median 38 months
Conflict of interest/source of funding	This study was supported by funding from the National Natural Science Foundation of China and the Distinguished Young Scholar Cultivation Project of Xijing Hospital. There were no conflicts of interest.

Analysis

Follow-up issues:

- All patients were either seen in the clinic or contacted by telephone to check for clinical status and adverse events after hospital discharge. TTE was used to evaluate improvements in the construction and function of the patient's heart at 3 months, 6 months, and 12 months after the procedure.

- The length of follow up was shorter in the transcatheter group because the centres started using this technique in 2010.

Study design issues: All demographic, valve-related, procedural and outcome data, and clinical and anatomical data were obtained from a retrospective review of patient charts and procedural records.

Study population issues:
- There were statistically significantly more patients with a left ventricular ejection fraction of less than 40 % in the transcatheter group than in the surgery group at baseline (16% [11/68]) compared with 3% (2/63), p=0.0041).
- In the transcatheter group there were 34 aortic PVL, 30 mitral PVL, 2 combined aortic and mitral PVL and 1 tricuspid PVL.

Key efficacy findings

Number of patients analysed: 131 (68 percutaneous PVL closure versus 63 surgical repair)

In-hospital outcomes and procedural characteristics

Clinical outcome	Transcatheter group	Surgery group	p value
Procedural success* rate	98% (67/68)	-	**-**
In-hospital mortality rate	0%	10% (6/63)	**<0.001**
Procedural time (minutes)	54 ± 36	358 ± 88	**0.011**
ICU stay (days)	0	2–9 (4.3 ± 2.1)	**<0.001**
Hospital length of stay (days)	7.9 ± 5.3	38.1 ± 42.2	**0.002**
Patients needing blood transfusion	16% (11/68)	100% (63/63)	**<0.001**

*Procedural success was defined as proper deployment of the device that resulted in significant reduction in regurgitation to mild-to-moderate or less residual regurgitation, without interference with the prosthesis or need for emergent surgery.

- In the surgery group, 17 patients had PVL repairs, and 46 patients had valve re-replacements. Five patients had a third open-heart operation because of residual regurgitation, and one patient had successful percutaneous closure after a repeat open-heart operation.

- In the transcatheter group, PVL regurgitation was decreased to mild and mild to moderate immediately after the procedure in all patients. There was a statistically significant decrease in the mean volume of PVL regurgitation from 10.1 ml ± 2.9 ml before the procedure to 1.6 ml ± 1.7 ml after the procedure, p<0.01.

NYHA functional class at 1 year

Clinical outcome	Transcatheter group	Surgery group	p value

% of patients with NYHA class improvement of 1 or more at 1-year follow up	82% (55/67)	68% (39/57)	-

Key safety findings

Perioperative complications

Clinical outcome	Transcatheter group	Surgery group
Haemolysis	6% (4/68) **	-
Femoral pseudoaneurysm***	3% (2/68)	-
Haemothorax *** (after a transapical approach)	1% (1/68)	-
Sepsis	-	8% (5/63)
Acute renal insufficiency [a]	-	6% (4/63)
Postoperative haemorrhage [b]	-	3% (2/63)
Low cardiac output syndrome	-	8% (5/63)

** Two of these patients had acute renal insufficiency and needed continuous renal replacement therapy and blood transfusions. All these patients recovered before discharge.

*** The patients recovered before hospital discharge.

[a] The patients needed continuous renal replacement therapy.

[b] The patients had haemostasis treatment.

Mortality during follow-up outcomes

Clinical outcome	Transcatheter group	Surgery group
Number of deaths	3	4

- In the transcatheter group, 1 patient died of recurrent haemolysis 5 months after the procedure, 1 patient died suddenly of no specific reason 6 months after the procedure and 1 patient died of heart failure 6 months after the procedure.

In the surgical group, 2 patients died of heart failure 12 and 20 months after the operation; 3 patients had severe haemolysis because of recurrent paravalvular regurgitation and had a third operation; and 2 patients died in the hospital after the third open-heart operation.

Study 9 Palaparti R (2019) – Conference abstract

Study details

Study type	Retrospective case series
Country	India (single centre)
Recruitment period	6-year period (no further details reported)
Study population and number	n=45 patients with PVL
Age and sex	Range 6 to 78 years; 71% (32/45) male
Patient selection criteria	Not reported
Technique	Transcatheter closure of PVL Devices used: ADO, ADO II, AVP, AVP II, AVP III, AVP IV, mVSD and Occlutech PLD device. Retrograde access was used for all aortic PVL. Transseptal access was used in 17/36 mitral leaks and percutaneous transapical access was used in 19/36. Fourteen patients in the apical group also had an additional transseptal access. All apical punctures were closed with additional plugs.
Follow up	Not clear from abstract
Conflict of interest/source of funding	Not reported

Analysis

Study population issues: The target valve was mitral in 31 patients (68.9%), aortic in 9 (20%), or both in 5 patients (11.1%).

Key safety findings

Adverse events after the procedure and during follow up

Adverse event	% patients
Haemothorax	11% (5/45)
Cerebrovascular accident	2% (1/45)
Acute kidney injury	11% (5/45)
After load mismatch	2% (1/45)
Device embolisation	4% (2/45) 1 needed surgery for failed procedure
Infective endocarditis	2% (1/45)
Death	7% (3/45) 2 happened during follow up

Study 10 Mijangos-Vazquez R (2016)

Study details

Study type	Case report
Country	Mexico
Recruitment period	Not reported
Study population and number	n=1 patient with an anterolateral leak in the mitral prosthesis
Age and sex	48 years; female
Patient selection criteria	Not reported
Technique	Percutaneous closure of a mitral paravalvular leak with transseptal puncture Device used: Amplatzer Vascular Plug (AVP III 10/5 mm).
Follow up	2 months
Conflict of interest/source of funding	None

Key safety findings

Aortic perforation

The patient had a history of rheumatic mitral valve disease. She had 3 previous mitral valve replacements. Her last echocardiogram reported an anterolateral leak in the mitral prosthesis. Catheterisation was done. During the procedure, when attempting to do the transseptal puncture, catheterisation was complicated by a forceful puncture of the aortic root by the Brockenbrough needle followed by an immediately advancement of an 8-Fr Mullins sheath. The medical team decided to leave the 8-Fr sheath in the aortic root recognising the danger of removing the sheath and advanced a 6/4 mm Amplatzer ductal occluder (ADO I) through the Mullins sheath and under fluoroscopy and TEE guidance the device was successfully deployed and the perforation was closed. Subsequently, the paravalvular leak was closed with an Amplatzer Vascular Plug (AVP III 10/5 mm).

Validity and generalisability of the studies

- The included systematic review and meta-analysis was selected as it was the most recent one, with the biggest sample size, including comparative studies and case series.
- There were no randomised studies identified and only retrospective studies were identified.
- Three non-randomised studies were included in the main extraction table and others were included in the systematic review and meta-analysis by Busu et al. (2018).
- The comparative studies compared percutaneous closure with surgical repair.
- There were several devices used within the studies. Some of them were used off-label. Several devices could be used to close one PVL.
- The longest follow up was a mean of 4 years.
- There were 3 registries included in the main extraction table: a UK and Irish one, a Spanish one and one including 9 countries (Italy, Poland, Lithuania, France, Hungary, Kazakhstan, Cyprus, Morocco and Romania).
- One single case report and 1 conference abstract were included for the safety data.
- There were no studies looking at quality-of-life outcomes.
- The patients included in the studies usually had severe medical conditions and comorbidities.
- There seems to be a learning curve associated with the procedure and Study 7 looked at this.
- All studies but 2 (Alkhouli et al. 2017 and the case report by Mijangos-Vazquez et al. 2016) looked at both mitral and aortic paravalvular leaks.

Existing assessments of this procedure

- The European Society of Cardiology and the American College of Cardiology Foundation published an expert statement on clinical trial principles and endpoint definitions for paravalvular leaks in surgical prosthesis in 2017.[8, 9]

- The American Heart Association and the American College of Cardiology task force on clinical practice guidelines published a focused update report of the 2014 AHA/ACC Guideline for the management of patients with valvular heart disease in 2017.[10] It said:

  '' *Percutaneous repair of paravalvular regurgitation is reasonable in patients with prosthetic heart valves and intractable hemolysis or NYHA class III/IV HF who are at high risk for surgery and have anatomic features suitable for catheter-based therapy when performed in centers with expertise in the procedure. [Class of recommendation 2A; level of evidence B].* ''

Related NICE guidance

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

Interventional procedures

- Valve-in-valve TAVI for aortic bioprosthetic valve dysfunction. NICE interventional procedures guidance 653 (2019). Available from http://www.nice.org.uk/guidance/IPG653
- Percutaneous mitral valve leaflet repair for mitral regurgitation. NICE interventional procedures guidance 649 (2019). Available from http://www.nice.org.uk/guidance/IPG649
- Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. NICE interventional procedures guidance 541 (2015). Available from http://www.nice.org.uk/guidance/IPG541
- Percutaneous mitral valve annuloplasty. NICE interventional procedures guidance 352 (2010). Available from http://www.nice.org.uk/guidance/IPG352

- Thoracoscopically assisted mitral valve surgery. NICE interventional procedures guidance 245 (2007). Available from http://www.nice.org.uk/guidance/IPG245

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two professional expert questionnaires for percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure. One patient organisation representing patients who have had this procedure provided submissions and these were discussed by the committee.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- One of the companies manufacturing a device used for this procedure wrote: ''The committee may need to be aware that there are surgically implanted valves and percutaneously implanted valves and different products may or may not be CE marked for both, despite their use. ''

- Aortic and mitral paravalvular leaks are considered together in this overview. The procedures are quite different, and the evidence base may vary between the 2 valve types.

- Ongoing trials:

- NCT03003481 Follow-up Registry to Monitor the Efficacy and Safety of the Occlutech PLD Device. N=500. Italy. Estimated study completion date: January 2021.
- NCT04489823 PARADIGM: Amplatzer Valvular Plug for PVL Closure (PARADIGM). Case series. N=200. Estimated study completion date: December 2023. Estimated study start date: November 2020.

References

1. Busu T, Alqahtani F, Badhwar V et al. (2018) Meta-analysis Comparing Transcatheter and Surgical Treatments of Paravalvular Leaks. The American journal of cardiology 122(2): 302-309
2. Alkhouli M, Rihal C S, Zack C J et al. (2017) Transcatheter and Surgical Management of Mitral Paravalvular Leak: Long-Term Outcomes. JACC. Cardiovascular interventions 10(19): 1946-1956
3. Zhang Y, Pan X, Qu X et al. (2019) Comparison of transcatheter and surgical treatment of paravalvular leak: Results from a 5-year follow-up study. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 94(2): e88-e95
4. Garcia E, Arzamendi D, Jimenez-Quevedo P et al. (2017) Outcomes and predictors of success and complications for paravalvular leak closure: an analysis of the SpanisH real-wOrld paravalvular LEaks closure (HOLE) registry. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 12(16): 1962-1968
5. Calvert P A, Northridge D B, Malik I S et al. (2016) Percutaneous device closure of paravalvular leak. Circulation 134(13): 934-944
6. Onorato E M, Muratori M, Smolka G et al. (2020) Midterm procedural and clinical outcomes of percutaneous paravalvular leak closure with the Occlutech Paravalvular Leak Device. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 15(14): 1251-1259
7. Sorajja P, Cabalka A K, Hagler, Donald J et al. (2014) The learning curve in percutaneous repair of paravalvular prosthetic regurgitation: an analysis of 200 cases. JACC. Cardiovascular interventions 7(5): 521-9
8. Yang C, Liu Y, Tang J et al. (2020) Prognosis of Transcatheter Closure Compared with Surgical Repair of Paravalvular Leak after Prosthetic Valve Replacement: A Retrospective Comparison. Thoracic Cardiovascular Surgeon 68:148–157
9. Ruiz C E, Hahn R T, Berrebi A et al. (2018) Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis. European heart journal 39(15): 1224-1245
10. Ruiz C E, Hahn R T, Berrebi, A et al. (2017) Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis: An Expert Statement. Journal of the American College of Cardiology 69(16): 2067-2087

11. Nishimura RA, Otto CM, Bonow RO, et al. (2017) AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol. 70:252–89.

Literature search strategy

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	09/02/2021	Issue 2 of 12, February 2021	0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	09/02/2021	Issue 2 of 12, February 2021	5
MEDLINE (Ovid)	09/02/2021	1946 to February 08, 2021	83
MEDLINE In-Process (Ovid)	09/02/2021	1946 to February 08, 2021	219
MEDLINE Epubs ahead of print (Ovid)	09/02/2021	1946 to February 08, 2021	42
EMBASE (Ovid)	09/02/2021	1974 to 2021 February 08	218

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

1 (Paravalvul* adj3 leak*).tw.
2 PVL.tw.
3 ((periprosthet* or prosthet* or regurgitat*) adj3 paravalvul*).tw. (679)
4 or/1-3
5 (TAVR or TAVI).tw.
6 ((trans-apic* or transapic or transarter* or trans-arter* or transcutan* or trans-cutan* or transfemor* or trans-femor*) adj3 aortic valve replace*).tw.
7 ((transcathet* or trans-cathet* or percutan* or device* or intervention*) adj3 (close* or closure* or treat* or reduction* or repair*)).tw.
8 (Amplatzer adj3 plug*).tw.
9 AVP.tw.
10 or/5-9
11 4 and 10
12 occlutech PLD.tw.
13 11 or 12
14 Animals/ not Humans/
15 13 not 14
16 limit 15 to ed=20191201-20210228

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies. The case series with 10 patients or less were not included.

Additional papers identified

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Al-Hijji M A, Alkhouli M S, Sarraf M et al. (2017) Characteristics and outcomes of re-do percutaneous paravalvular leak closure. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 90(4): 680-689	Comparative study n=16 re-do percutaneous PVL closure versus 48 age- and sex-matched first percutaneous PVL closure FU=30 days	Re-do percutaneous PVL closure is feasible with favorable procedural success rate and low 30-day MACE. Development of new paravalvular defects is the most common indication for re-do PVL closure, highlighting the importance of careful longitudinal monitoring and follow-up.	Studies with more patients or longer follow-up are already included.
Alkhouli M, Sarraf M, Maor E et al. (2016) Techniques and outcomes of percutaneous aortic paravalvular leak closure. JACC. Cardiovascular interventions 9(23): 2416-2426	Case series n=80 Mean FU=27 months	Percutaneous reduction of aortic PVL is associated with durable symptom relief and lower rates of repeat cardiac surgery. The magnitude of benefit is greatest with PVL reduction to a grade of mild or less. Therefore, attempts should be made to reduce PVL as much as possible.	Patients may already be included in Alkhouli (2017) and this study is included in the Busu (2018) systematic review and meta-analysis.
Alkhouli M, Zack C J, Sarraf M et al. (2017) Successful percutaneous mitral paravalvular leak	Case series n=231	70% (162) patients had ≤mild PVL after the procedure. Compared with those who had >mild residual PVL,	Most patients may be included in Alkhouli (2017) that is included in the main

closure is associated with improved midterm survival. Circulation. Cardiovascular interventions 10(12)	Median FU=2 years	patients with ≤mild residual PVL had lower rates of repeat surgical interventions (6% versus 17%; p=0.004) and lower all-cause mortality at 30 days (1% versus 14%; p<0.001) and 1 year (15% versus 39%; p<0.001). Survival at 3 years was 61% in patients who had ≤mild residual leak and 47% in patients with higher grade of residual PVL (p=0.002).	extraction table. Other studies with more patients or longer follow-up are already included.
Ando Tomo, Takagi H for the ALICE (All-Literature Investigation of Cardiovascular Evidence) Group (2016) Percutaneous Closure of Paravalvular Regurgitation After Transcatheter Aortic Valve Implantation: A Systematic Review. Clinical cardiology 39(10): 608-614	Systematic review Search from 2002 to 2015 n=58 patients from 14 studies	-Mean success rate: 87% -The median number of closure devices used was 1 (range, 1–4) -Seven patients had history of valve-in-valve and 6 patients had procedural success. -Among the patients with available follow-up data (95%), there were 15 deaths (27%).	Studies with more patients are included.
Angulo-Llanos R, Sarnago-Cebada F, Rivera A R et al. (2016) Two-Year Follow Up After Surgical Versus Percutaneous Paravalvular Leak Closure: A Non-Randomized Analysis. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography &	Retrospective comparative study n=87 (51 percutaneous versus 36 surgical) Mean follow-up: 784.6 days	- Hospital mortality was higher in the surgical group (30.6% vs. 9.8%, OR 6, p=0.01). - Clinical improvement was higher in the percutaneous group (71.4% vs. 36.4%, p= 0.002). - There were no differences in survival free from the composite end-point if al-cause mortality or readmission according to the treatment	This study is included in the Busu (2018) systematic review and meta-analysis.

Interventions 88(4): 626-634		received (surgical or percutaneous).	
Azevedo A I, Braga P, Rodrigues A et al. (2017) Percutaneous closure of periprosthetic paravalvular leaks: A viable alternative to surgery?. Revista portuguesa de cardiologia: orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology: an official journal of the Portuguese Society of Cardiology 36(78): 489-494	Retrospective case series n=18 (20 procedures) Follow-up=2 years	- Technical success: 75% (15/18) of procedures. - At discharge, median NYHA functional class decreased by 1 and haemolytic anaemia decreased from 7 patients (38.9%) to 2 (11.1%). - Two patients had minor bleeding at the femoral vascular access site. -Survival rates at 6, 12 and 24 months were 77.8%, 77.8% and 61.1%, respectively.	Studies with more patients or longer follow-up are already included.
Cortes M, Garcia E, Garcia-Fernandez M A et al. (2008) Usefulness of transesophageal echocardiography in percutaneous transcatheter repairs of paravalvular mitral regurgitation. The American journal of cardiology 101(3): 382-6	Case series n=27 Follow-up= 3 months	TEE is a fundamental technique when considering the percutaneous treatment of paravalvular leaks in patients with high surgical risk. It provides essential information on the characteristics of the dehiscence during implantation and follow-up.	Studies with more patients or longer follow-up are already included.
Cruz-Gonzalez I, Rama-Merchan J C, Calvert P A et al. (2016) Percutaneous Closure of Paravalvular Leaks: A Systematic Review. Journal of interventional cardiology 29(4): 382-92	Systematic review 13 studies	- Technical success: 77% to 86% - Clinical success: 67% to 77%	Studies with more patients or longer follow-up are already included.
Cruz-Gonzalez I, Rama-Merchan J C,	Case series	-Successful device implantation: 94% (in 2	This study is included in the

Arribas-Jimenez A et al. (2014) Paravalvular leak closure with the Amplatzer Vascular Plug III device: immediate and short-term results. Revista espanola de cardiologia (English ed.) 67(8): 608-14	n=33 Follow-up=90 days	patients, a second planned procedure was needed) -Successful closure (regurgitation reduction ≥1 grade): 91% -Complications included emergency surgery due to disc interference (n = 1) and blood transfusion (n = 3) -At 90 days, survival was 100%, and 90.3% of patients showed significant clinical improvement; 4 patients developed vascular complication (pseudoaneurysm).	Busu (2018) systematic review and meta-analysis.
Dhoble A, Chakravarty T, Nakamura M et al. (2017) Outcome of paravalvular leak repair after transcatheter aortic valve replacement with a balloon-expandable prosthesis. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 89(3): 462-468	Retrospective comparative study n= 72 (15 PVL repair versus 27 no repair) Mean follow-up=19 months (PVL repair) versus 22 months (no repair)	-Successful PVL repair: 87% patients -In patients with successful PVL repair, there was an improvement in symptom status, subsequent hospitalisations, and B-type natriuretic peptide levels. -There was 1 (out of 13, 8%) death in the group of patients who successfully had PVL repair whereas 24 (out of 57, 42%) patients died during follow-up in the group that did not have the procedure. - There was significant reduction in the subsequent heart failure related hospitalisation after PVL repair,	Studies with more patients or longer follow-up are already included.

		compared with the no-repair group (p=0.03).	
Franco E, Almeria C, de Agustin J A et al. (2014) Three-dimensional color Doppler transesophageal echocardiography for mitral paravalvular leak quantification and evaluation of percutaneous closure success. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 27(11): 1153-63	Retrospective case series n=40 Median follow-up=7.4 months	-Technical success rate: 76.9% -1-year estimated survival: 69.5% -Closure device undersizing according to 3D color ERO length, but not other PVL measurements, was significantly associated with PVL closure failure (p = 0.007).	Studies with more patients or longer follow-up are already included.
Giblett J P, Rana B S, Shapiro L M et al. (2019) Percutaneous management of paravalvular leaks. Nature reviews. Cardiology 16(5): 275-285	Review	Although sparse, data indicate that percutaneous closure of PVL is a safe and effective alternative to surgical closure, with similar long- term morbidity and mortality. Although large-scale, randomised data are needed to define the safety and efficacy of percutaneous closure of PVL, the procedure has become the first- line treatment in clinical practice in experienced centres. The procedure is intricate and requires the involvement of an experienced structural heart team to optimize the likelihood of success.	Review
Goktekin O, Vatankulu, M A, Ozhan H et al.	Case series	-Early post-procedural outcome was uneventful	This study is included in the

(2016) Early experience of percutaneous paravalvular leak closure using a novel Occlutech occluder. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 11(10): 1195-200	n=21 Follow-up=17.5 months	in all cases, with 1 or more grade reduction in regurgitation in all patients. -There was no mortality during hospital stay. -Complications: 1 haemothorax and 1 pneumothorax -No deaths were recorded during follow-up. -One patient had a reintervention and was treated successfully with the same device 11 months after the index procedure.	Busu (2018) systematic review and meta-analysis.
Hein R, Wunderlich N, Robertson G et al. (2006) Catheter closure of paravalvular leak. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2(3): 318-25	Case series n=21 Mean follow-up=13.5 months	-Technical success for device implantation: 95% -Immediate residual leak: 85% -Significant shunting persisting during follow up: 45% -Complications: a permanent leaflet obstruction was observed in one patient. Severe complications during follow-up led to early death in 1 patient and surgical intervention in 3. -A successful second catheter treatment was done in 3 patients. -The event-free survival from re-operation, death and stroke at the end of the observation period was 80%.	Studies with more patients or longer follow-up are already included.

Jabbar AA, Hasan M, Jenkins JS et al. (2020) Elective Percutaneous Paravalvular Leak Closure Under Conscious Sedation: Procedural Techniques and Clinical Outcomes. Cardiovascular Revascularization Medicine; 21 (10); 1291-1298	Retrospective cohort study n=37 patients (54 PVLs, 65% aortic & 35% mitral) had elective catheter-based repair.	Procedural technical success was 81% in the overall cohort and 88% in the aortic group. No procedural deaths but short-term mortality during the first 30 days was 5.4% (two patients). Use of conscious sedation with monitored anesthesia care resulted in short hospital stay.	Studies with more patients or longer follow-up are already included.
Jang SJ, Truong QA, Bergman G et al. (2021) Percutaneous Closure of Aortic and Mitral Paravalvular Leaks-Diagnostic and Therapeutic Considerations. Current Treatment Options in Cardiovascular Medicine; vol. 23 (no. 2); 19.	Review	PVL occurs in 6% to 15% of aortic valve and 7% to 17% of mitral valve procedures. Percutaneous device closure of PVL has shown an improved survival benefit and is associated with improved clinical outcomes. Multimodal imaging and inter-disciplinary discussion are essential for a high success rate of percutaneous closure of PVL. A PVL closure device with various available shapes might be helpful for increasing procedural success rates.	Review
Jian K, Wang Q, Zhang W et al. (2016) Percutaneous transcatheter closure of prosthetic paravalvular leaks. International Journal of Clinical and Experimental Medicine 9(7): 13595-13604	Case series n=13 Maximum follow-up=13 months	-Technical success: 12/13 patients. -The only major adverse event occurred in one patient whose sudden death we consider unrelated to the surgery. -Left ventricular end-diastolic diameter and pulmonary artery pressure were decreased significantly	This study is included in the Busu (2018) systematic review and meta-analysis.

		compared with pre-operation echocardiographic assessment (from 62.9±16.2 to 59.2±16.1 mm, and from 41.5±10.2 to 34.9±8.9 mmHg). -NYHA functional class was improved by at least 1 grade in 5 patients. -The patient survival rate after PVL closure was 83%. -Another death occurred 13 months after surgery because of progressive heart failure.	
Krishnaswamy A, Tuzcu EM and Kapadia SR (2014). Percutaneous paravalvular leak closure. Interventional cardiology; vol. 9 (1); 44-48.	Review	Large series on percutaneous approaches to PVL closure demonstrate high levels of procedural success and promising clinical outcomes. A thorough understanding of multimodality imaging is necessary for the diagnosis of PVL and the safe and successful performance of these closure procedures.	Review
Kilicgedik A, Gunduz S, Fedakar A. et al. (2017) Closure of mitral paravalvular defects without performing an arteriovenous loop: A case series of fourteen patients. Postepy w Kardiologii Interwencyjnej 13(4): 307-312	Case series n=14 Follow-up=not reported	Nineteen devices (10 (66.6%) via transseptal access; 4 (26.6%), transapical access; and 1 (6.6%), retrograde access) were deployed successfully without making an AV loop.	Studies with more patients or longer follow-up are already included.
Kozlowski M, Pysz P, Wojakowski W et al.	Prospective registry	Steerable sheaths are safe and effective	Studies with more patients or

(2019) Improved Transseptal Access for Transcatheter Paravalvular Leak Closure Using Steerable Delivery Sheaths: Data From a Prospective Registry. The Journal of invasive cardiology 31(8): 223-228	n=53 (31 steerable delivery sheath versus 22 control without steerable sheath) Follow-up=not reported	devices that support mitral PVL closure, particularly for challenging PVL locations.	longer follow-up are already included.
Millan X, Bouhout I, Nozza A et al. (2017) Surgery Versus Transcatheter Interventions for Significant Paravalvular Prosthetic Leaks. JACC. Cardiovascular interventions 10(19): 1959-1969	Comparative study n=231 (80 transcatheter reduction [TR] versus 151 surgical correction [SC]) Median follow-up=3.5 years	-SC was associated with an important reduction in all-cause death or hospitalisation for heart failure compared with TR (HR: 0.28; 95% CI 0.18 to 0.44; p < 0.001). -There was a trend towards reduced all-cause death following SC versus TR (HR: 0.61; 95% CI 0.37 to 1.02; p = 0.06). -Neither intervention normalised survival when compared with a general population or patients undergoing their first surgical valve replacement.	This study is included in the Busu (2018) systematic review and meta-analysis.
Millan X, Skaf S, Joseph L et al. (2015) Transcatheter reduction of paravalvular leaks: a systematic review and meta-analysis. The Canadian journal of cardiology 31(3): 260-9	Systematic review and meta-analysis. n=362 patients from 12 studies	A successful transcatheter PVL reduction was associated with a lower cardiac mortality rate (OR, 0.08; 95% credible interval [CrI], 0.01 to 0.90) and with a superior improvement in functional class or haemolytic anaemia, compared with a failed intervention (OR, 9.95; 95% CrI, 2.10-66.73). Fewer repeat surgeries	A more recent systematic review and meta-analysis is included.

		were also observed after successful procedures (OR, 0.08; 95% CrI, 0.01-0.40).	
Mookadam F, Raslan S F, Jiamsripong P et al. (2012) Percutaneous closure of mitral paravalvular leaks: a systematic review and meta-analysis. The Journal of heart valve disease 21(2): 208-17	Systematic review and meta-analysis. n=100 patients from 8 studies	-Cardiovascular mortality rate during 1st year of follow-up: 15% -Clinical success: 48% -Failures were attributed to deployment failure (18%), to a persistent leak, haemolysis or both (31%). -Procedure-related complication rate (bleeding, stroke, endocarditis): 16%	A more recent systematic review and meta-analysis is included.
Nijenhuis V J, Swaans M J, Post M C et al. (2014) Open transapical approach to transcatheter paravalvular leakage closure: a preliminary experience. Circulation. Cardiovascular interventions 7(4): 611-20	Case series n=37 Follow-up=1 year	-Procedure success: 86%. - Early safety at 30 days (event-free survival): 84%. -1-year survival rate: 66%. -NYHA functional class and quality of life significantly improved. -Clinical efficacy (survival free of stroke, rehospitalisation, NYHA 3/4, and device-related dysfunction): 49% at 3 months and 31% at 1 year. -Moderate to severe residual PVL was associated with all-cause mortality (HR 3.9; 95% CI 1.2 to 12.1; p=0.03).	Studies with more patients or longer follow-up are already included.
Noble S, Jolicoeur E M, Basmadjian A et al. (2013) Percutaneous paravalvular leak	Case series n=56	-Procedural success: 75% -Three major complications, including	This study is included in the Busu (2018) systematic

reduction: procedural and long-term clinical outcomes. The Canadian journal of cardiology 29(11): 1422-8	Follow-up=beyond 1 year	2 deaths, occurred during the initial 30-day follow-up in the 42 patients who were treated with a device. -After adjusting for the logistic EuroSCORE, prosthesis type (mitral vs aortic), and time interval since the last valve surgery, a successful percutaneous PVL reduction [PPVR] was associated with a better survival free of rehospitalisation for congestive heart failure, need for surgical reintervention, and death compared with patients with a failed PPVR. (HR: 0.34; 95% CI 0.17 to 0.71).	review and meta-analysis.
Okuyama K, Jilaihawi H, Kashif M et al. (2015) Percutaneous paravalvular leak closure for balloon-expandable transcatheter aortic valve replacement: a comparison with surgical aortic valve replacement paravalvular leak closure. The Journal of invasive cardiology 27(6): 284-90	Case series n=20 (10 post-TAVR and 10 post-SAVR patients) Mean follow-up= 46 days	-Nos severe complications reported. -Procedural success rate: 60% (post-TAVR) versus 100% (post-SAVR), p=0.04	Studies with more patients or longer follow-up are already included.
Panaich S S, Maor E, Reddy G et al. (2019) Effect of percutaneous paravalvular leak closure on hemolysis. Catheterization and cardiovascular	Retrospective case series n=168 patients with anaemia or abnormal	Percutaneous PVL closure is associated with modest improvement in haemolysis markers, increase in haemoglobin levels and reduction in	Studies with more patients or longer follow-up are already included

interventions: official journal of the Society for Cardiac Angiography & Interventions 93(4): 713-719	haemolysis markers Median follow-up (for blood transfusions only) =4.6 years	blood transfusion requirements. This benefit is most significant in patients with mechanical valves.	
Pinheiro C, Passos R, Daniele C, Eduardo P et al. (2016) Paravalvular Regurgitation: Clinical Outcomes in Surgical and Percutaneous Treatments. Arquivos brasileiros de cardiologia 107(1): 55-62	Retrospective comparative study n=35 (10 percutaneous versus 25 surgical) Follow-up=1 year	-During hospitalisation, both groups had many complications (74.3%), with no statistically significant difference in the analysed outcomes. -After 1 year, the percutaneous group had more re-interventions (20% vs 8.7%, p = 0.57) and a higher mortality rate (20% vs 0%, p = 0.08). -A high incidence of residual mitral leak was observed after the percutaneous procedure (50% vs 8.7%, p = 0.08).	This study is included in the Busu (2018) systematic review and meta-analysis.
Ruiz C E, Jelnin V, Kronzon I et al. (2011) Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. Journal of the American College of Cardiology 58(21): 2210-7	Retrospective case series n=43 Follow-up=42 months	-Successful closure 86% -28/35 patients improved by at least 1 NYHA functional class. - % patients needing blood transfusions or erythropoietin injections: 56% (before the procedure) versus 5% (after the procedure) -Clinical success: 89% -Survival rates at 6, 12 and 18 months: 92%, 89% and 87%.	This study is included in the Busu (2018) systematic review and meta-analysis.

		-Freedom from cardiac-related death at 42 months: 92%	
Ruiz C E, Chi-Hion L, Vladimir J et al. (2017) Hopscotch technique: A novel method for percutaneous closure of paravalvular leaks. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 89(5): 944-950	Retrospective case series n=15 Follow-up=not reported	-Procedural success: 12/15 - Mild or less residual mitral paravalvular regurgitation: 93% of procedures	Studies with more patients or longer follow-up are already included.
Ruparelia N, Cao J, Newton J D et al. (2018) Paravalvular leak closure under intracardiac echocardiographic guidance. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 91(5): 958-965	Retrospective case series n=18 Follow-up=1 year	-Successful PVL closure: 78% -No intracardiac echocardiographic-related complications. -79% patients reported symptomatic improvement of at least 1 NYHA class and the remaining patients had no change. -Death within 30 days of the procedure: 1/18 -1-year survival: 71%	Studies with more patients or longer follow-up are already included.
Saia F, Martinez C, Gafoor S et al. (2015) Long-term outcomes of percutaneous paravalvular regurgitation closure after transcatheter aortic valve replacement: a multicenter experience. JACC. Cardiovascular interventions 8(5): 681-8	Case series n=24 Mean follow-up: 12 months	-Successful procedures: 89% -Cumulative survival rates at 1, 6 and 12 months were 83%, 67% and 62 % respectively. -Most of the deaths were of noncardiac causes (8/11).	Studies with more patients or longer follow-up are already included.

Sanchez-Recalde A, Moreno R, Galeote G et al. (2014) Immediate and mid-term clinical course after percutaneous closure of paravalvular leakage. Revista espanola de cardiologia (English ed.) 67(8): 615-23	Case series n=20 Mean follow-up=13 months	-Successful implantation rate: 87% -Successful procedure rate: 83% -Survival rate at 1 year: 65% -Survival rate free of death/ surgery: 59% - The degree of residual regurgitation was not associated with mortality but was associated with functional status. -Survivors showed significant improvement in functional class.	This study is included in the Busu (2018) systematic review and meta-analysis.
Shapira Y, Hirsch R, Kornowski R et al. (2007) Percutaneous closure of perivalvular leaks with Amplatzer occluders: feasibility, safety, and shortterm results. The Journal of heart valve disease 16(3): 305-13	Case series n=11 Follow-up=6 to 24 months	-Successful device deployment rate: 91% patients -Failure to cross the leak: 1/11 -Interruption of mitral leaflet movement: 2/11 -Decreased leakage rate: 60% -Residual leak: 10/11 -Haemolysis was reduced in 4 patients, increased in 4 and unchanged in 2. -Improved NYHA functional class of 1 grade: 5/11 -One patient needed a 2nd procedure to seal a residual leak.	Studies with more patients or longer follow-up are already included.
Smolka G, Pysz P, Wojakowski W et al. (2013) Clinical manifestations of heart failure abate with transcatheter aortic paravalvular leak closure using	Prospective registry n=17	Heart failure caused by aortic PVL can be safely and efficiently treated with transcatheter PVL closure using AVP II and III devices as occluders.	Studies with more patients or longer follow-up are already included.

Amplatzer vascular plug II and III devices. The Journal of invasive cardiology 25(5): 226-31	Follow-up=6 months		
Smolka G, Pysz P, Kozlowski M et al. (2016) Transcatheter closure of paravalvular leaks using a paravalvular leak device - A prospective Polish registry. Postepy w Kardiologii Interwencyjnej 12(2): 128-134	Prospective registry n=30 Follow-up=30 days	-Device success rate: 94% -Procedural success: 94% - During the follow-up period there was an increase of haemoglobin concentration (3.9 to 4.1 g/dl), red blood count (11.6 to 12.2 M/mm3) and functional improvement by NYHA class.	Studies with more patients or longer follow-up are already included.
Smolka G, Pysz P, Jasinski M et al. (2016) Multiplug paravalvular leak closure using Amplatzer Vascular Plugs III: A prospective registry. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 87(3): 478-87	Prospective registry n=49 Follow-up=12 months	-Transcatheter PVL closure was done in 46 patients (93.9%) with 78% acute procedural success rate. -When successful, it led to a significant decrease of NT-proBNP concentration and heart failure symptoms regression. -Periprocedural safety endpoints were met in 3 patients and included non-disabling stroke, and 2 access site-related complications. -In device failure group 2 patients died (end-stage heart failure) and 2 were rehospitalised.	This study is included in the Busu (2018) systematic review and meta-analysis.
Smolka G, Pys, P, Ochala A et al. (2017) Transcatheter paravalvular leak closure and hemolysis - A prospective	Prospective registry n=79	Risk factors for PVL-related haemolysis were the presence of calcifications in the defect and mitral location of PVL. The	Studies with more patients or longer follow-up are already included.

registry. Archives of Medical Science 13(3): 575-584	Follow-up=6 months	TPVLC effectively reduced haemolysis if at least 90% reduction of PVL cross sectional area was achieved. The effect was sustained in 6-month follow-up. Incomplete closure of PVL may increase the magnitude of haemolysis after TPVLC, but it occurred rarely.	
Sorajja P, Cabalka A K, Hagler D J et al. (2011) Long-term follow-up of percutaneous repair of paravalvular prosthetic regurgitation. Journal of the American College of Cardiology 58(21): 2218-24	Retrospective case series n=126 Mean follow-up=17 months	-Estimated survival rate at 3 years: 64% -Mortality rate: 10% (cardiac cause), 7% (noncardiac), 6% (unknown). - 72% of survivors who had presented with heart failure were free of severe symptoms and need for cardiac surgery. - For those with no, mild, or moderate or severe residual regurgitation, 3-year estimate of survival free of death or need for surgery was 63%, 58%, and 30% (p= 0.01), respectively.	Studies with more patients or longer follow-up are already included.
Sorajja P, Cabalka A K, Hagler D J et al. (2011) Percutaneous repair of paravalvular prosthetic regurgitation: acute and 30-day outcomes in 115 patients. Circulation. Cardiovascular interventions 4(4): 314-21	Case series n=115 Follow-up=30 days	Devices were implanted in 125 defects (89% of total defects), including in 19 patients with multiple defects. Successful percutaneous closure rate: 88/115 (77%) patients. 30-day complication rate: 9% (sudden and unexplained death, 2%;	Studies with more patients or longer follow-up are already included.

		stroke, 3%; emergency surgery, 1%; bleeding, 5%). Two devices embolised during the procedure and were retrieved without sequelae. No procedural deaths occurred, but 2 (2%) patients died by 30 days.	
Tanner R, Hassan S, Ryan N et al. (2019) Trans-catheter paravalvular leak closure: a single-centre experience. Irish journal of medical science 188(2): 489-496	Retrospective case series n=21 Mean follow-up=22 months	Clinical success: 86% -30-day mortality rate: 0%. There was 1 major adverse complication (stroke). Deaths during follow-up: 28% (6).	Studies with more patients or longer follow-up are already included.
Taramasso M, Maisano F, Latib A et al. (2014) Conventional surgery and transcatheter closure via surgical transapical approach for paravalvular leak repair in high-risk patients: results from a single-centre experience. European heart journal cardiovascular Imaging 15(10): 1161-7	Case series n=17 (transcatheter closure only Median follow-up= 21 months (transcatheter closure only)	For transcatheter closure only: acute procedural success: 94%. Severe acute kidney injury: 1/17. In-hospital death: 0%	Studies with more patients or longer follow-up are already included.
Venturini J M, McClelland I, Blair J E A et al. (2019) Percutaneous Transapical Left Ventricular Access to Treat Paravalvular Leak and Ventricular Septal Defect. The Journal of invasive cardiology 31(9): 247-252	Retrospective case series n=13 Follow-up=6 months	Procedural success: 100%. One access-site complication occurred, involving embolism of a duct occluder into the pleural space and extravasation from the apical puncture site. Haemostasis of the apex site was achieved immediately with placement of 3 vascular plugs from a femoral	Studies with more patients or longer follow-up are already included.

		approach. Two patients died before hospital discharge and neither death was related to a procedural complication. There were no significant pericardial effusions.	
Waterbury T M, Reeder G S, Pislaru S V et al. (2017) Techniques and outcomes of paravalvular leak repair after transcatheter aortic valve replacement. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 90(5): 870-877	Retrospective case series n=18 Follow-up=1 month	In selected patients, percutaneous PVL repair following TAVR is feasible and effective for both balloon expandable and self-expanding prostheses. Most patients undergoing PVL closureafter TAVR require a single occluder plug placement for reduction in PVL to mild or less.	Studies with more patients or longer follow-up are already included.
Wells J A 4th, Condado J F, Kamioka N et al. (2017) Outcomes After Paravalvular Leak Closure: Transcatheter Versus Surgical Approaches. JACC. Cardiovascular interventions 10(5): 500-507	Retrospective comparative study n=114 (56 transcatheter versus 58 surgical PVL closure) Follow-up=1 year	The transcatheter group had a shorter post-operative stay (4 vs 8 days; p < 0.001), a shorter intensive care unit stay (0 vs 3 days; p < 0.001), and fewer readmissions at 30 days (8.9% vs 25.9%; p= 0.017). There were no differences in the primary endpoint (33.9% vs SI 39.7%; p = 0.526) or 1-year survival (83.9% vs 75.9%; p= 0.283) between groups.	This study is included in the Busu (2018) systematic review and meta-analysis.
Yildirim A, Goktekin O, Gorgulu S et al. (2016) A New Specific Device in Transcatheter Prosthetic Paravalvular Leak Closure: A	Prospective case series n=52 (32 off-label device [group 1] versus 20	The procedural success rate was 100% (29 of 29 leaks) in group 2 while the rate was 92% (39 of 42 leaks) in group 1. However, more	This study is included in the Busu (2018) systematic review and meta-analysis.

Prospective Two-Center Trial. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 88(4): 618-624	Occlutech [group 2]) Follow-up=not reported	secondary events were observed in group 1, but they did not reach statistical significance (8 vs. 1, p=0.064).	
Zorinas A, Janusauskas V, Davidavicius G et al. (2018) Retrospective analysis of single-center early and midterm results of transapical catheter-based mitral paravalvular leak closure with a purpose-specific device. Postepy w Kardiologii Interwencyjnej 14(2): 167-175	Retrospective case series n=19 Follow-up=1 year	Technical, device and individual patient success at follow-up was achieved in 18 (95%), 16 (84%) and 16 (84%) patients respectively. Median intensive therapy unit stay was one day (1–4) and mean hospital stay was 11 ±4 days. A reduction of paravalvular regurgitation to a mild or lesser degree was achieved in 18 (95%) patients. There were no strokes or myocardial infarctions at follow-up. There were no deaths at 30 days after the procedure. One (5%) patient died from progression of heart failure 12 months after surgery.	Studies with more patients or longer follow-up are already included