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A focus on the percutaneous therapy of mitral and tricuspid regurgitation

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While mitral stenosis of rheumatic origin has been effectively treated percutaneously for more than 20 years, transcatheter treatment of mitral (MR) and tricuspid (TR) regurgitation appears as a contemporary unmet clinical need. The advent of new transcatheter therapies offers several treatment options for elderly and frail patients at high surgical risk. MitraClip is now consolidated as a therapy for functional MR in selected patients. Transcatheter mitral valve replacement is a promising alternative to transcatheter repair, for both functional and degenerative forms. However, further developments and new evidence are needed. Transcatheter treatment of the tricuspid valve has arrived late compared to similar technologies that have been developed for the aortic and mitral valve, and is currently in its infancy. This is likely due, in part, to the previously underreported impact of TR on patient outcomes. Edge-to-edge repair is the most advanced transcatheter solution in development. Data on annuloplasty and tricuspid valve replacement are limited and more evidence is needed. The future looks promising for transcatheter mitral and tricuspid valve therapies, although their place in clinical practice has yet to be clearly defined.

Introduction

Mitral regurgitation

Worldwide, ~24 million people are affected by primary (or degenerative) mitral regurgitation (PMR).[1] This has as its main cause myxomatous degeneration resulting in prolapse of one or both valve leaflets. Secondary (or functional) mitral regurgitation (SMR) accounts for ~65% of isolated moderate or severe mitral regurgitation (MR) cases and is not associated with valvular morphological alterations, but with pathological dilatation of one or both left cardiac chambers. Approximately 24% of patients with left ventricular dysfunction have severe SMR.[1]

Regardless of comorbidities and left ventricular function, moderate or severe MR is associated with increased mortality.[1]

Tricuspid regurgitation

Moderate or severe tricuspid regurgitation (TR) has a prevalence of 4% in subjects 75 years of age or older and is associated with increased all-cause mortality. The secondary or functional form accounts for 90% of cases and is often the result of left heart chamber disease or atrial fibrillation.[1]

Indications

Mitral regurgitation

The 2021 ESC/EACTS guidelines recommend valve repair as the first line surgical treatment in severe grade PMR (I, B), when durable results are expected following the surgery.[2] Transcatheter treatment of severe PMR by edge-to-edge devices is recommended (IIb, B) in symptomatic patients who meet the echocardiographic eligibility criteria and who, after evaluation by the Heart Team, are deemed inoperable or at high surgical risk.[2] In patients with severe SMR, symptomatic despite optimal medical therapy, transcatheter treatment using 'edge-to-edge' devices is recommended with Class of recommendation IIa, level of evidence B, if clinical and echocardiographic criteria suggestive of significant benefit following interventional treatment are met.[2]

If the above criteria are not met, treatment using edge-to-edge is recommended (IIb, C) in selected cases after evaluation by the Heart Team.[2]

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Table 1 Devices most used in clinical practice for transcatheter repair of mitral valve and tricuspid valve

Device	MitraClip/Triclip	Pascal	Carillon	Cardioband	MitrAlign/TriAlign
					
Indication	PMR[a]/SMR[a] TR	PMR[a]/SMR TR	SMR[a]	SMR TR	SMR TR
Technique	Edge-to-edge	Edge-to-edge	Indirect annuloplasty	Direct annuloplasty	Direct annuloplasty
CE mark	Yes/yes	Yes/yes	Yes	Yes/yes	Yes/—
Advantages	- Numerous supporting studies - Wide choice of devices	- Central spacer - Possibility of contextual repair of mitral and tricuspid with the same device	- No transseptal puncture for MR - Combined treatment (edge-to edge)	- Can also be used in very dilated annuli - Adaptable to the patient - Combined treatment (edge-to edge)	- No transseptal puncture for MR
Disadvantages	- Transseptal puncture for MR - Risk of iatrogenic stenosis	- Transseptal puncture for MR - Risk of iatrogenic stenosis	- Risk of coronary artery compression	- Transseptal puncture for MR - Complexity and duration of the procedure	- Few scientific evidence to support it

PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TR, tricuspid regurgitation.
[a]Randomized controlled clinical trial to support the indication.

Tricuspid regurgitation

Surgical treatment is indicated (I, C) in patients with severe primary or secondary TR requiring cardiac surgery for left valvular disease or in case of isolated severe primary TR in the absence of severe right ventricular dysfunction. For patients with severe secondary TR considered surgically inoperable, percutaneous treatment in centres with experience in the treatment of tricuspid pathologies is indicated (IIb, C).[2]

Transcatheter mitral valve repair

The distinction between PMR and SMR is relevant, playing an important role in choosing the most suitable device to use.

Numerous transcatheter devices are available that mimic the various surgical repair techniques. The most used devices in clinical practice are undergoing continuous improvement, while other systems are in the preclinical testing phase (*Table 1*).

They can be divided into: edge-to-edge repair systems, direct annuloplasty, indirect annuloplasty, and chordal repair.

Edge-to-edge repair systems

MitraClip

The edge-to-edge surgical valve repair technique consists in joining the two mitral leaflets, in their central portions (scallops A2–P2), with a suture, determining the formation of a double orifice mitral valve. The first transcatheter device to adopt Alfieri's edge-to-edge technique was the MitraClip system (Abbott Vascular), consisting of a cobalt-chromium metal clip with two arms equipped with two internal 'tweezers' (grippers) in the shape of U necessary to be able to grasp the valve leaflets.

It obtained the CE mark in 2008.

The EVEREST II randomized trial 'Endovascular Valve Edge-to-Edge Repair Study' compared MitraClip and surgical repair in almost all patients with PMR (72%). The study showed a superiority in 30-day safety with the MitraClip, but with a similar mortality rate. Long-term follow-up has shown higher rates of moderate-to-severe or severe MR and increased need for mitral valve surgery after MitraClip.[3] Post-approval registries have focused predominantly on SMR. The ACCESS-EU registry highlighted the safety and clinical efficacy of Mitraclip in a high-risk surgical population affected by SMR (69%). At 12 months, less than moderate MR remained in 79% of patients. Additionally, there was significant improvement in functional status. Two randomized-controlled trials evaluated the effect of MitraClip in patients with heart failure (HF) with reduced ejection fraction and moderate-severe or severe SMR compared to optimized medical therapy alone. The two trials reported apparently contradictory results in terms of clinical outcomes. The COAPT trial 'Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation' showed a convincing therapeutic benefit of MitraClip, while the MITRA-FR trial did not show substantial differences.[4,5] The different designs of the two trials have provided explanations for these discrepancies. HF therapy

was examined prior to enrolment in the COAPT study, whereas medical therapy optimization continued throughout the MITRA FR.[4,5] The MR cut-off for study enrolment was higher in the COAPT (EROA > 0.4 cm^2) than the MITRA FR (EROA > 0.2 cm^2).[4,5] In addition, a maximum cut-off of left ventricular dilatation was required in the COAPT for enrolment.[4] These nuances have led to fundamentally different patient phenotypes and study populations characterized by greater left ventricular dilatation and less severe MR in MITRA FR compared to less dilated left ventricles but more severe MR in COAPT.[6] SMR is found to be disproportionate in COAPT, but more proportionate in MITRA FR; MitraClip could be particularly effective in reducing disproportionate SMR.[6] Therefore, the 2021 ESC/EACTS Guidelines on the Management of Valvular Heart Disease have strengthened the COAPT echocardiographic criteria and defined the appropriate mitral anatomy to be treated with MitraClip as EF: 20–50%, left ventricular end-systolic diameter <70 mm, and pulmonary artery pressure <70 mmHg.[2,4]

An international registry, Mitra-Bridge, has also highlighted the value of MitraClip in patients with moderate-to-severe SMR and end-stage HF awaiting a heart transplant or LVAD.[7]

The recent updates of the device (MitraClip G4), now in its 4th generation, have introduced: the possibility of independent 'grasping' of the leaflets, four types of clips to be adapted to different valve anatomies, and the 'real-time' evaluation of the left atrial pressure from the guide catheter. The 30-day results from the EXPAND G4 post-marketing registry, which enrolled over 1000 patients with PMR or SMR, showed that 89% of patients achieved a reduction in impairment grade from moderate-severe or severe to mild or less.

The REPAIR MR trial is currently ongoing and will compare the clinical results of MitraClip device with surgical repair in patients with severe PMR at moderate surgical risk, providing new evidence on the impact of the device in degenerative forms.

Pascal

The Pascal system (Edwards Lifescience) is conceptually identical to the MitraClip, entirely manufactured in nitinol. The device consists of a central spacer (spacer) around which there are paddles and clasps that allow capturing the valve leaflets. The safety and efficacy CLASP study 'The CLASP Study Edwards PASCAL TrAnScatheter Mitral Valve RePair System Study' enrolled 124 patients, of whom 31% and 69% had PMR and SMR, respectively.[8] At the two-year follow-up, the procedural success rate was 94%, with reduction of MR to moderate or less in 97% of patients and with 93% of subjects in NYHA Class I or II. In addition, there was a significant decrease in left ventricular volume.[8]

PASCAL Ace is a further version of the device, introducing more size options, with a thinner central spacer.

Results from CLASP IID study, the first randomized trial comparing PASCAL vs. MitraClip in patients with severe or moderate-severe symptomatic PMR, were recently published.[9] A pre-specified interim analysis in 180 patients demonstrated the non-inferiority of the PASCAL system vs. MitraClip for the primary safety and efficacy endpoints of serious adverse event rate (3.4% vs. 4.8%) and reduction of MR to moderate or less (96.5% vs. 96.8%). At six months, the rates of reduction of MR were comparable across groups, with results that tend slightly to favour Pascal.[9]

The results of CLASP IIF, the other arm of the trial that will recruit patients with SMR, are awaited.

Transcatheter tricuspid repair

Surgical treatment of isolated tricuspid valve disease is quite rare, in consideration of the high post-operative mortality (~5% to 10%) and due to the frequent surgery ineligibility of these patients. Therefore, several transcatheter technologies have recently been developed to address this clinical need.

Edge-to-edge systems

TriClip

Initially the MitraClip system was adapted for edge-to-edge repair of the tricuspid valve. Subsequently, through modifications of the guide catheter and the delivery catheter, the TriClip device (Abbott Vascular) was created and designed for treating the tricuspid valve. The new version of the device (TriClip G4) has the same equipment as Clips (four different models), different in length and width of the arms, of the 'cousin' MitraClip G4.

Results from the single-arm TRILUMINATE trial, at both 6 and 12 and 24 months of follow-up, demonstrated a significant and sustained reduction in TR, with only 40% of 48 patients with available 2-year data showing TR compared to 97% baseline.[10] In addition, there was a significant reduction in unplanned hospitalizations for HF compared to the year prior to device implantation and a low rate of adverse events.[10]

The preliminary results of the first 200 patients enrolled in the bRIGHT 'real world' registry were recently presented. It showed acute procedural success (defined as a reduction in TR of at least one grade) in 88% of patients. Of the 115 patients available for 30-day follow-up, 90% showed improvements of at least one degree in TR. Additionally, there was a significant improvement in functional status. The TRILUMINATE pilot trial will provide, for the first time, a clinical comparator to a tricuspid valve transcatheter therapy.

Pascal

The Pascal system (Edwards Lifescience) is identical to that used for edge-to-edge mitral valve repair. By virtue of a 'case series' for compassionate use, it obtained the CE mark in 2020.

The results of the CLASP TR feasibility study highlighted a procedural success of 88% and a low rate of adverse events. At a 1-year follow-up, 86% of patients had moderate or less residual TR, with an overall improvement in functional status.[11]

The second study of the CLASP TR will randomize 825 subjects with at least severe and symptomatic TR to receive either transcatheter repair with the Pascal system or medical therapy alone.

Annuloplasty

Mitral annuloplasty

Cardioband

The Cardioband device (Edwards Lifesciences) allows direct annuloplasty to be performed via transcatheter by

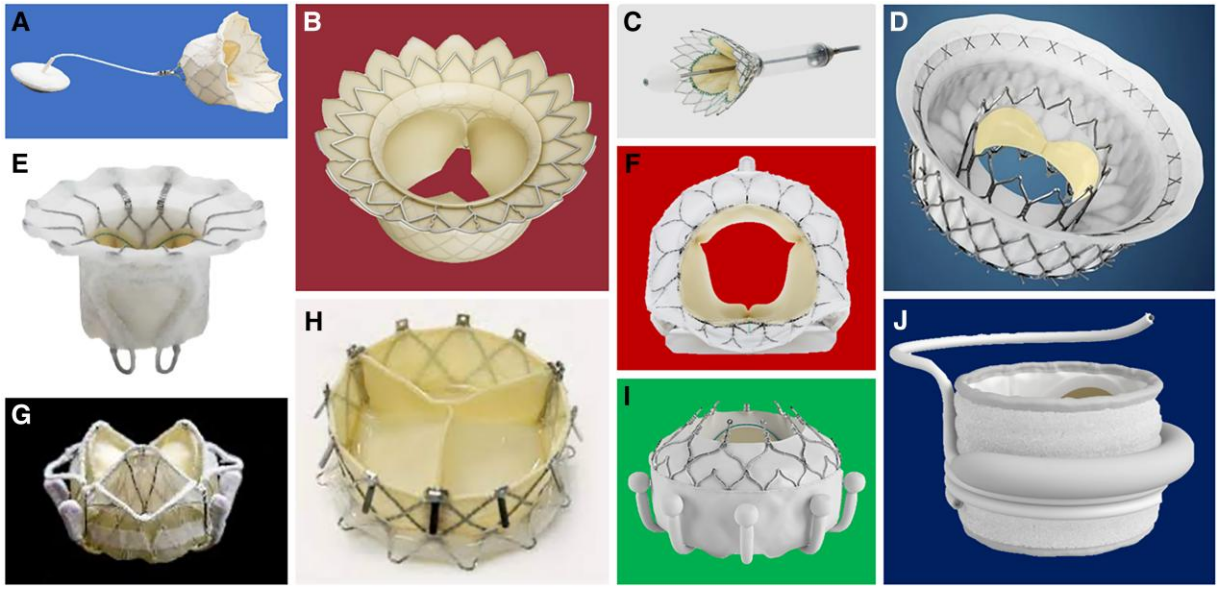

Figure 1 Devices for transcatheter mitral valve replacement. (*A*) Tendyne* (Abbott), (*B*) HighLife Bioprosthesis and Subannular Implant (HighLife SAS), (*C*) Cardiovalve (Cardiovalve), (*D*) Intrepid (Medtronic), (*E*) FORTIS (Edwards Lifesciences), (*F*) Tiara (Neovasc Inc.), (*G*) Caisson (LivaNova), (*H*) NaviGate (NaviGate Cardiac Structures Inc.), (*I*) EVOQUE (Edwards Lifesciences), (*J*) SAPIEN M3 (Edwards Lifesciences). *CE mark.

fixing it to the mitral annulus, using 12 or 17 metal anchors of a polyester band. After anchoring it to the annulus, the device can be adapted according to the individual anatomy, to obtain a reduction of the annular diameters and the regurgitant volume. Its use in clinical practice is still limited by the technical complexity of the procedure, the long learning curve, and the presence of few scientific data to support it.

Carillon

The Carillon indirect mitral annuloplasty device (cardiac dimension) consists of a nitinol connector with, at its ends, two self-expanding anchors, to be positioned inside the coronary sinus, and the great cardiac vein. This device is implanted via jugular access and determines the reduction of the mitral annulus by external compression. The REDUCE-FMR trial 'Safety and Efficacy of the CARILLON Mitral Contour System® in Reducing Functional Mitral Regurgitation (FMR) Associated With Heart Failure' demonstrated the efficacy of the device, successfully implanted in 94% of patients, obtaining a significant reduction in regurgitant volume and left ventricular volumes.[12]

Tricuspid annuloplasty

Cardioband

The Cardioband device, used in the tricuspid position, appears to date being a promising system for the treatment of valve anatomies with large coaptation gaps that would make a suboptimal repair using edge-to-edge systems. Efficacy and safety were examined in the TRIREPAIR study 'TrIcuspid Regurgitation RePAIr With CaRdioband Transcatheter System', highlighting a procedural success of 100% and a low rate of adverse events. In the 2-year follow-up, a 16% reduction in the lateral septum diameter was achieved, with 72% of patients having less than moderate residual TR.[13] Its use in clinical practice is still limited by the technical complexity and long learning curve.

Chordal repair

Various chordae tendon implantation devices have been developed for the treatment of patients with PMR. To date, the only device that has obtained the CE mark is NeoChord DS1000 (NeoChord), which, by means of a transapical approach, allows the fixation of one or more neochords to the prolapsed flap and ventricular wall. This device has shown a procedural success rate of 97% and a significant reduction in the degree of regurgitation.[14] Studies regarding the new transseptal approach techniques are underway to evaluate their applicability in clinical practice.

Valve replacement

Transcatheter mitral and tricuspid valve replacement is a new and growing field (*Figures 1* and *2*). Devices and techniques developed must overcome procedural and anatomical obstacles such as device anchorage and left ventricular outflow tract obstruction. Proper patient selection and careful planning of the procedure will favour the development of this solution, with greater procedural and clinical success.

Mitral valve replacement

The only CE-marked transcatheter mitral valve replacement device is the Tendyne Mitral Valve System (Abbott Vascular). Self-expanding valve system implanted via transapical access, the stability of this system is also ensured by the presence of a connector that fixes it to the apex of the left ventricle. The efficacy of the device was evaluated in a prospective multicenter registry of 100 patients, almost all (89%) with severe or moderate-

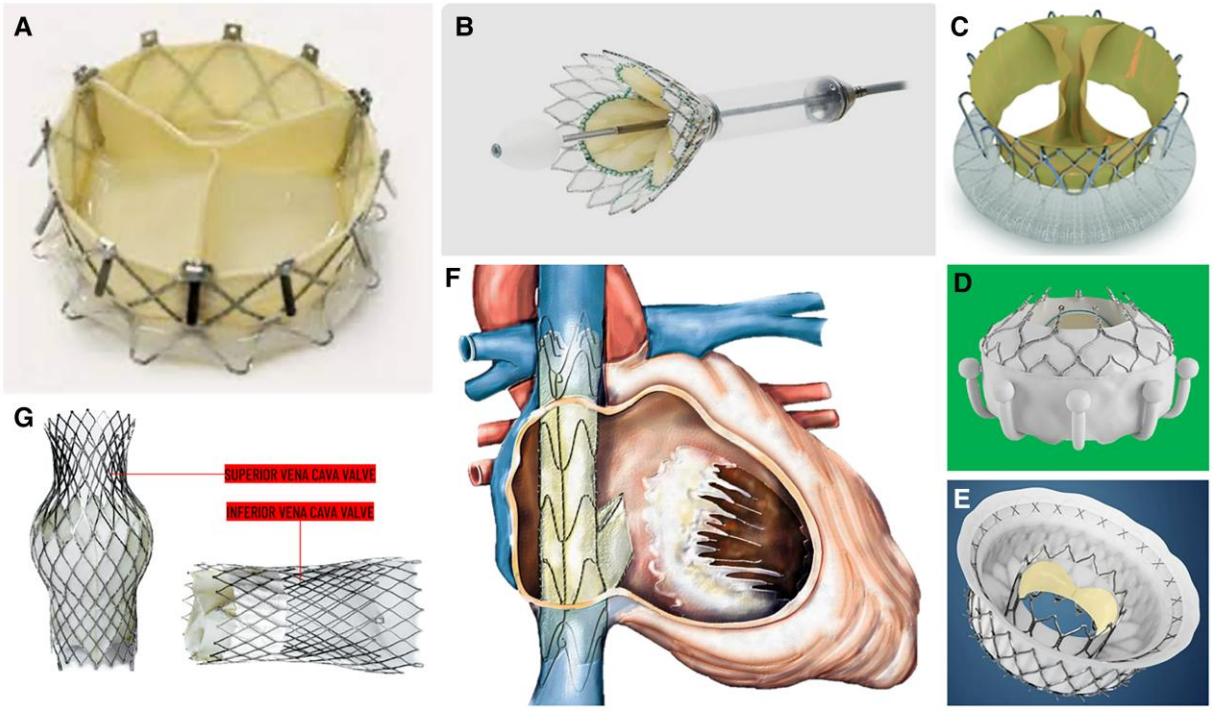

Figure 2 Devices for transcatheter tricuspid valve replacement and caval systems. (*A*) NaviGate (NaviGate Cardiac Structures Inc.), (*B*) Cardiovalve (Cardiovalve), (*C*) Trisol (Trisol Medicam), (*D*) EVOQUE (Edwards Lifesciences), (*E*) Intrepid (Medtronic), (*F*) Tricento (NVT), (*G*) TricValve* (OrbusNeich P&F). *CE mark.

severe SMR or mixed grade.[15] It showed a procedural success of 97% and, at 2 years follow-up, a significant reduction in hospitalizations for HF, NYHA class and MR degree, with total absence of regurgitation in 93.2% of cases.[15] The use of this device is still limited by the difficulty in patient selection and the risk arising from transapical access.

The SAPIEN 3 self-expanding valve (Edwards Lifesciences) was designed for aortic valve replacement, but is used off-label in the mitral position in case of implantation inside degenerated prostheses (valve-in-valve, ViV), surgical rings (valve-in-ring, ViR), and severely calcified annulus (valve-in-MAC, ViMAC) via transseptal access. The best results, in terms of technical and procedural success of the device, were obtained in the case of ViV compared to ViR and ViMAC.

A version specifically designed for the mitral valve, the SAPIEN M3, has been developed.

Numerous preclinical trials are underway, the results of which are expected in the coming years.

Tricuspid valve replacement

Tricuspid valve replacement makes use of devices currently used mainly for compassionate use (*Figure 2*). They can be divided into two categories: orthotopic implanted devices and heterotopic implanted devices (caval systems).

Orthotopic valves

Orthotopic implant devices are often devices initially conceived for mitral valve replacement, such as EVOQUE (Edwards Lifesciences) and Intrepid (Medtronic), and more rarely, as in the case of the Trisol Valve (Trisol Medical), developed specifically for the tricuspid valve.

Heterotopic valves

The rationale for their use lies in the reduction of caval reflux in patients with severe TR. The currently available heterotopic valves are the TricValve (OrbusNeich P&F), which obtained the CE mark in 2021 and the Tricento (NVT). The first is composed of a prosthetic valve positioned in the superior vena cava (SVC) and one in the inferior vena cava (IVC), while the second is composed of a single stent that is positioned between the SVC and IVC, with a bicuspid valve in bovine pericardium in lateral position.

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Data availability

No new data were generated or analysed in support of this research.

References

1. Coffey S, Roberts-Thomson R, Brown A *et al*. Global epidemiology of valvular heart disease. *Nat Rev Cardiol* 2021;**18**:853–864.

2. Vahanian A, Beyersdorf F, Praz F; ESC/EACTS Scientific Document Group, ESC National Cardiac Societies *et al*. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2022; **43**:561–632.
3. Feldman T, Kar S, Elmariah S, EVEREST II Investigators *et al*. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol* 2015;**66**: 2844–2854. doi:10.1016/j.jacc.2015.10.018
4. Stone GW, Lindenfeld J, Abraham WT, COAPT Investigators *et al*. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.
5. Obadia JF, Messika-Zeitoun D, Leurent G, MITRA-FR Investigators *et al*. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;**379**:2297–2306.
6. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging* 2019;**12**:353–362.
7. Godino C, Munafò A, Scotti A *et al*. Mitraclip in secondary mitral regurgitation as a bridge to heart transplantation: 1-year outcomes from the International MitraBridge Registry. *J Heart Lung Transplant* 2020;**39**: 1353–1362.
8. Webb JG, Hensey M, Szerlip M *et al*. 1-year outcomes for transcatheter repair in patients with mitral regurgitation from the CLASP study. *JACC Cardiovasc Interv* 2020;**13**:2344–2357.
9. Lim DS, Smith RL, Gillam LD, CLASP IID Pivotal Trial Investigators *et al*. Randomized comparison of transcatheter edge-to-edge repair for degenerative mitral regurgitation in prohibitive surgical risk patients. *JACC Cardiovasc Interv* 2022;**15**:2523–2536.
10. Lurz P, Stephan von Bardeleben R, Weber M, TRILUMINATE Investigators *et al*. Transcatheter edge-to-edge repair for treatment of tricuspid regurgitation. *J Am Coll Cardiol* 2021;**77**:229–239.
11. Kodali S, Hahn RT, Eleid MF, CLASP TR EFS Investigators *et al*. Feasibility study of the transcatheter valve repair system for severe tricuspid regurgitation. *J Am Coll Cardiol* 2021;**77**:345–356.
12. Witte KK, Lipiecki J, Siminiak T *et al*. The REDUCE FMR trial: A randomized sham-controlled study of percutaneous mitral annuloplasty in functional mitral regurgitation. *JACC Heart Fail* 2019;**7**:945–955.
13. Nickenig G, Weber M, Schüler R *et al*. Tricuspid valve repair with the cardioband system: two-year outcomes of the multicentre, prospective TRI-REPAIR study. *EuroInterv* 2021;**16**:e1264–e1271.
14. Colli A, Manzan E, Aidietis A *et al*. An early European experience with transapical off-pump mitral valve repair with NeoChord implantation. *Eur J Cardiothorac Surg* 2018;**54**:460–466.
15. Muller DWM, Sorajja P, Duncan A *et al*. 2-year outcomes of transcatheter mitral valve replacement in patients with severe symptomatic mitral regurgitation. *J Am Coll Cardiol* 2021;**78**:1847–1859.