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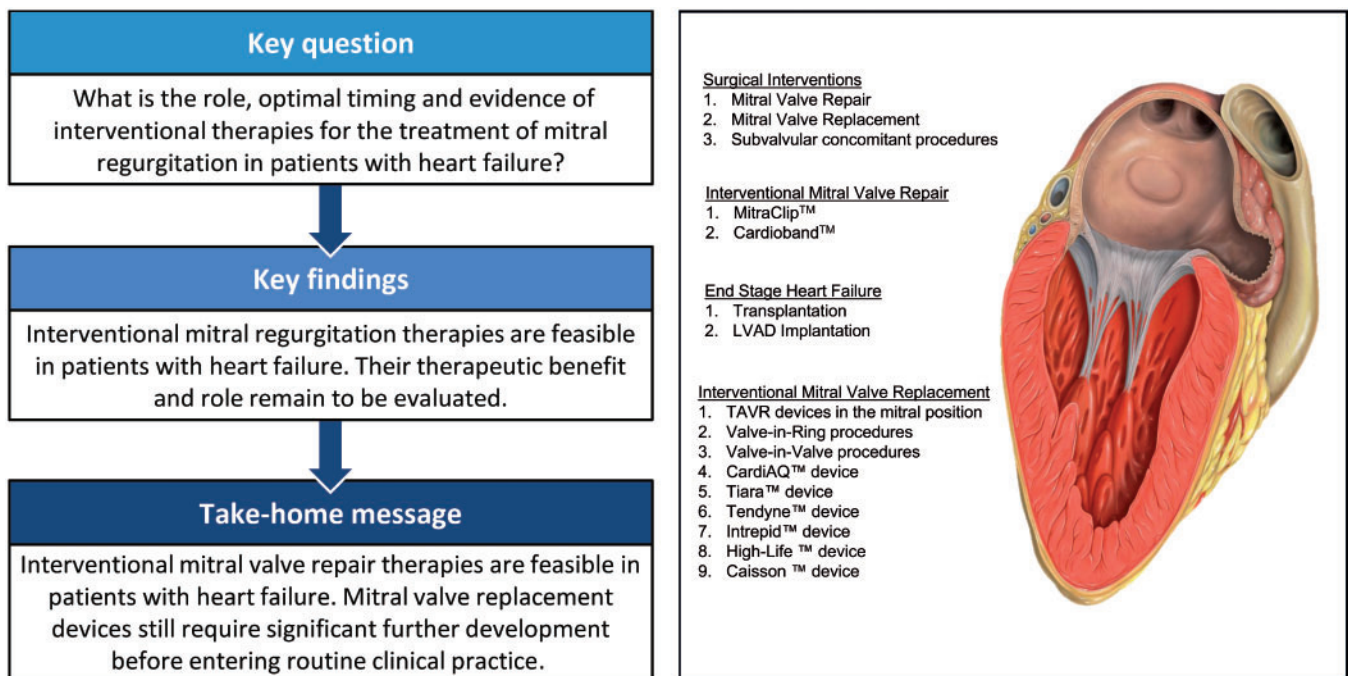
# The role of transcatheter mitral valve therapy in heart failure

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## Summary

Mitral valve regurgitation is detected in up to 75% of patients with heart failure. Interventional mitral valve therapies can be used to treat mitral regurgitation with very low morbidity and mortality rates and minimal invasiveness. Devices intended for the replacement of the mitral valve still require significant development and refinement before entering clinical practice on a large scale. The derived benefit of these therapies, the priority (repair over replacement) and the therapeutic role in patients with secondary mitral regurgitation due to heart failure remain to be investigated.

**Keywords:** Mitral valve regurgitation • Mitral interventions • Heart failure

## HEART FAILURE DEMOGRAPHICS

Heart failure (HF) is a complex clinical syndrome characterized by the reduced ability of the heart to pump and/or fill with blood, which results in inadequate cardiac output to meet metabolic demands or adequate cardiac output secondary to compensatory neurohormonal activation. HF has been characterized as a global pandemic, affecting more than 28 million people worldwide, and as a significant burden on each nation's total

health expenditure, a burden that is expected to more than double in the next 20–25 years [1, 2].

## Incidence of mitral regurgitation in congestive heart failure

Mitral regurgitation (MR) is detected in up to 75% of patients with HF of various stages, severities and aetiologies [3]. MR is classified as 'primary' ('organic' or 'degenerative') when the insufficiency of

the mitral valve (MV) is caused by structural or degenerative defects and abnormalities of the MV apparatus (leaflets, chordae tendineae, papillary muscles or mitral annulus). In contrast, in 'secondary' MR (also known as 'functional'), the insufficiency of the MV occurs in the absence of organic or structural mitral disease and is usually due to left ventricular (LV) dysfunction. The causes that lead an apparent structurally normal MV to become insufficient are multifactorial. Usually, LV dilatation leads to mitral annulus dilatation with various degrees of displacement of the subvalvular mitral apparatus, whereas the MV is structurally intact. LV dilatation leading to secondary MR can be of ischaemic or non-ischaemic aetiology. Ischaemic secondary MR denotes the occurrence of MR in the presence of significant coronary artery disease, resulting either from regional wall motion abnormality with papillary muscle dysfunction or from ischaemic cardiomyopathy with global LV dysfunction. Non-ischaemic secondary MR occurs in dilated cardiomyopathy. Secondary MR without LV dysfunction can also occur in patients with restrictive cardiomyopathies and chronic atrial fibrillation; however, these pathophysiological conditions are relatively rare [3].

Patients with secondary MR have a significantly poorer prognosis relative to that of patients with LV dysfunction who do not have MR in patients with ischaemic as well as non-ischaemic cardiomyopathy. MR and chronic LV systolic dysfunction are independent predictors of mortality leading to significantly lower survival rates at up to 5 years in patients with HF who have at least moderate MR [4]. Even only moderate MR has been shown to independently and significantly predict worse survival in patients with ischaemic as well as non-ischaemic cardiomyopathy [5, 6].

### Surgical therapies for secondary mitral regurgitation

In an attempt to mimic the result of surgery and MV repair in primary MR, MV repair with restrictive ring annuloplasty has been developed and thoroughly examined over the last 20 years. By implanting an undersized, rigid, complete ring, a reduction of the MV annulus can be achieved, leading to improved leaflet coaptation. However, this technique treats only the dilatation of the MV annulus as the sole culprit of the secondary MR, while ignoring the subannular components of the MV whose relative distortion with respect to each other has a significant influence on the development of secondary MR. Subvalvular procedures, such as secondary chordal cutting and papillary muscle repositioning or approximation, are not widespread, and there is little experience with these techniques and their results [7–9]. Although surgical revascularization in patients with ischaemic cardiomyopathy is beneficial [10], significant reductions in secondary MR cannot be expected solely from revascularization in all patients [11]. Furthermore, correction of moderate MR at the time of surgical revascularization did not prove to be beneficial in several well-designed studies [12, 13]. For patients with severe ischaemic MR, MV repair was not superior to MV replacement in terms of survival and LV remodelling and was associated with significant MR recurrence and rehospitalization rates [14].

### Interventional transcatheter devices for treatment of mitral regurgitation in patients with heart failure

The main focus of interventional devices for the treatment of secondary MR is either to repair the MV with the goal of restoring

valve competency or to completely replace the closure mechanism by implanting a valve inside the native MV. Although to date most interventional MV devices and device trials focus on high-surgical-risk patients with primary MR or on a mixture of high-risk patients with primary and secondary MR, without an explicit focus on secondary MR, several key results from these devices are applicable in patients with HF and secondary MR.

## MITRAL REPAIR DEVICES

### Edge-to-edge repair

The MitraClip™ device (Abbott Vascular, Santa Rosa, CA, USA) has been the cornerstone for the treatment of MR in patients with high surgical risk with more than 80 000 implantations worldwide. Mimicking the Alfieri surgical technique, the clip is implanted via a transfemoral venous puncture and grasps the anterior mitral leaflet and posterior mitral leaflet at the site of MV regurgitation, creating a double-orifice MV, eliminating the majority of the regurgitation jet.

Although data from prospective randomized trials with the MitraClip device in patients with HF with secondary MR are lacking, most randomized trials and registries have included a variable proportion of patients with HF and secondary MR. In the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) trial, only 27% of the patients randomized to either surgery or MitraClip therapy had secondary MR [15, 16]. Although an apparent efficiency benefit (death, reoperation and freedom from severe MR) for the MitraClip group could be shown at 4 years for patients with degenerative MR, no difference in efficiency for the subgroup with secondary MR could be shown, possibly indicating that the underlying ventricular dysfunction has a much larger prognostic significance in patients with HF and secondary MR than the symptomatic resolution of secondary MR [15, 16]. Results from several registries show that although MitraClip implantation in patients with HF and secondary MR is feasible and can lead to improvement in functional status, no clear survival improvement could be observed [17–19]. Several trials are currently underway to evaluate the role of MitraClip therapy in patients with HF and secondary MR [7]. Data from recently published randomized multicentre studies have been controversial. In the European MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) study, patients who had percutaneous MV repair and medical therapy did not show a significant benefit in terms of survival or unplanned hospitalization for HF at 1 year in comparison to patients who received medical therapy alone [20]. In contrast to the findings of the MITRA-FR study, the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial showed that among patients with HF and moderate-to-severe or severe secondary MR who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, transcatheter MV repair resulted in a lower rate of hospitalization for HF and lower all-cause mortality within 24 months of follow-up than medical therapy alone [21]. It remains difficult to explain the different results obtained from the MITRA-FR and the COAPT trials and draw clinically important conclusions. The challenge of the future will be to clearly define the patient population with a high degree of functional MR that has the highest potential for long-term improvement in symptoms and rates of mortality and rehospitalization.

## Direct annuloplasty

The goal of the Cardioband™ technique (Edwards Lifesciences, Irvine, CA, USA) is to provide an interventional, non-surgical alternative to the concept of restrictive annuloplasty, which has been the cornerstone of surgical therapy for the treatment of secondary MR. Through a transfemoral venous puncture and a transseptal access, a flexible band is implanted along the posterior MV annulus between the left and right fibrous trigones. Fixation of the flexible band along the annulus is performed using anchors that are screwed through the band in the fibrous and muscular tissue of the posterior MV ring, under simultaneous assessment with fluoroscopy and echocardiography. After implantation of the device, the flexible band can be actively contracted, reducing the annulus diameter until resolution of the MR is achieved. The experience and results with this device are limited, and no results or comparisons exist, other than feasibility trials [22–24]. An advantage of the Cardioband system is that it targets a different mechanism of MR (annular dilatation) while not precluding treatments such as MitraClip implantation in case of combined diseases or residual MR [24]. Significant calcification of the MV ring or proximity of the circumflex artery to the MV annulus can preclude successful implantation of the device. However, both disease states can be identified from the preoperative examination of the heart using computed tomography.

## Mitral valve replacement devices

Because no interventional MV repair device can simultaneously address the multifactorial aetiology of secondary MR and the fact that a non-negligible proportion of patients develop recurrent MR after interventional MV repair [22, 23, 25], the transcatheter replacement of the MV and transcatheter MV implantation have been topics of intense research. However, the development of a prosthesis for the mitral position is significantly more challenging than the successful replacement of the transcatheter aortic valve. Several challenges still impede the development of a safe and easy method for implanting a transcatheter MV prosthesis such as the non-circular-shaped mitral annulus geometry, the lack of rigid structures for the deployment and securing of the device and the risk of left ventricular outflow tract (LVOT) obstruction.

## Transcatheter aortic valve replacement devices in the mitral position

In patients with significant major mitral annulus calcification, which may provide a rigid structure for the deployment of a properly sized transcatheter aortic valve replacement (TAVR), implantation of a balloon-expandable TAVR prosthesis has been shown to be a feasible option; however, it has been associated with significant morbidity (30% 30-day mortality) and low procedural success (72%) [26]. Although a significant proportion of this observed mortality can be attributed to the comorbidities these patients bring to the operation, these suboptimal results make this therapeutic option suitable only in patients with prohibitive operative risk or as a palliative therapy.

In patients with bioprosthetic valve degeneration after bioprosthetic MV replacement or in patients with recurrence of MR after MV repair, a reoperation carries a significant risk, and therefore, only a minority of patients are offered or referred for such a procedure. HF and significant LV dysfunction often

contribute a significant risk to the therapeutic options available for these patients.

The implantation of TAVR devices in patients with degenerated bioprosthetic valves in the mitral position offers a much less invasive alternative than reoperation, with satisfactory results. The balloon-expandable SAPIEN™ valve (Edwards Lifesciences) and to a lesser extent the mechanically expanding Lotus™ (Boston Scientific, Marlborough, MA, USA) have been implanted in degenerated MV prostheses [27–30]. The SAPIEN 3 valve has received approval of the Food and Drug Administration (FDA) for implantation in degenerated aortic and MV bioprostheses [valve-in-valve (ViV)]. Similarly, in patients with significant MR recurrence after MV repair, implantation of a TAVR device inside the mitral ring [valve-in-ring (ViR)] has shown to be a feasible option [29]. Significant advances in sizing, matching the right TAVR device and device size to the right surgical device and avoiding LVOT obstruction and TAVR device embolization have made ViV and ViR procedures acceptable therapies in patients with prohibitive and high operative risk. In the largest multicentre registry to date, the feasibility of implanting a TAVR device in the mitral position either as ViV or ViR could be shown, with satisfactory results up to 1 year postoperatively. In comparison to ViV, patients after ViR had significantly lower technical success rates and higher rates of morbidity and mortality, which persisted up to 1 year postoperatively [31].

## Development of transcatheter devices for mitral valve replacement

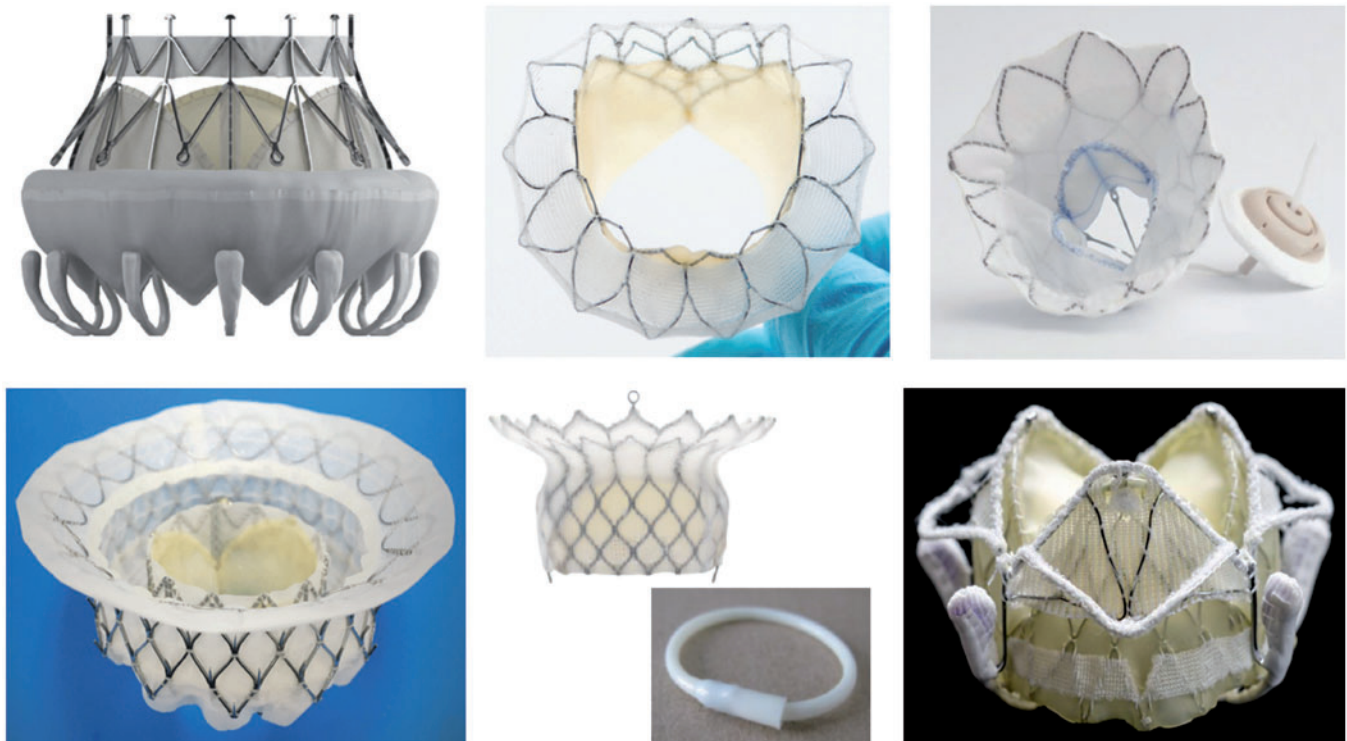
Data from surgical trials show that although MV repair confers significant advantages for the patient with primary MR [32], the benefit of MV repair versus MV replacement in patients with secondary MR and HF usually of ischaemic aetiology is less clear [14, 33]. The durability of repair after restrictive annuloplasty also remains a concern. With this in mind, several attempts are currently underway to develop an MV prosthesis for transcatheter mitral valve replacement (TMVR), which can be implanted either transapically or transvenously and transseptally.

Currently, 6 TMVR valves have been implanted in patients: the CardiAQ™ valve (Edwards Lifesciences, Irvine, CA, USA), the Tiara™ valve (Neovasc Inc., Richmond, BC, Canada), the Tendyne™ valve (Abbott Vascular, Santa Clara, CA, USA), the Intrepid™ valve (Medtronic, Minneapolis, MN, USA), the High Life™ valve (High Life, Paris, France) and the Caisson™ valve (LivaNova, Milan, Italy) (Fig. 1).

The CardiAQ device consists of a porcine pericardial bioprosthesis and can be delivered via a transseptal or transapical approach. Multiple anchors along the native leaflet tissue aim to secure the valve in place. The CardiAQ valve was the first TMVR device implanted in a human in 2012.

The Tiara device is a pericardial bovine prosthesis within a self-expanding stent. The device is implanted transapically via a 32-Fr or 36-Fr sheath. The device is D-shaped to minimize the risk for LVOT obstruction. The device is fixed in position with 2 ventricular tabs that engage the left and right fibrous trigones at the native valve commissures and 1 tab that interacts with the posterior shelf of the annulus at the P2 area.

The Tendyne device is a porcine valve also implanted via a transapical approach. The outer stent frame extends well above the plane of the annulus inside the left atrium. An apical pad



**Figure 1:** Transcatheter mitral valve replacement devices. Top line from left to right: the CardiAQ™ valve (Edwards Lifesciences, Irvine, CA, USA), the Tiara™ valve (Neovasc Inc., Richmond, BC, Canada) and the Tendyne™ valve (Abbott Vascular, Santa Clara, CA, USA). Bottom line from left to right: the Intrepid™ valve (Medtronic, Minneapolis, MN, USA), the High Life™ valve (High Life, Paris, France) and the Caisson™ valve (LivaNova, Milan, Italy).

assists in securing the device in place by means of active tethering.

The Intrepid valve consists of a dual stent design. A conformable outer stent engages the annulus and leaflets and provides fixation and sealing while isolating the inner stent from the dynamic anatomical environment. The circular inner stent houses a 27-mm tricuspid bovine pericardial valve. The valve is implanted using transapical access; transseptal access is under development.

The High Life valve uses arterial retrograde access across the aortic valve to place a ring around the chordal apparatus of the native MV that allows the valve stent to be anchored. The valve itself is delivered through transapical access.

The Caisson valve is intended only for transvenous–transseptal access. The stent consists of an anchor-like frame that is placed in the annulus of the MV, still allowing for valve function. In a second step, the valve itself is fixed to the anchor in the supra-annular position. A stent arm is then placed around the anterior leaflet in a position to prevent systolic anterior motion.

### Open questions in transcatheter mitral valve therapies

Although transcatheter MV therapies have been the focus of intensive research and the number of potential patients who may benefit from this development is far greater than the number of patients who benefit from TAVR, it is becoming clear that the MV is much more complex than the aortic valve. Since the first TMVR, fewer than 300 patients worldwide have been treated. The biggest challenge is patient selection. Because of the large size of the device stents, only a few patients qualify for secure implantation following anatomical considerations. Possible

obstruction of the LVOT after TMVR is the most common reason for rejection in TMVR trials. Transapical access may also limit the number of patients who can be treated safely. Due to the nature of the disease, patients with functional MR and ischaemic or dilative cardiomyopathy often have a reduced ejection fraction and a thin myocardial wall, conditions that increase the risk for myocardial damage during and after TMVR procedures. In the majority of TMVR studies, approximately 80% of screened patients had to be excluded for anatomical reasons.

In addition to such technical problems, several open questions remain: although transcatheter valve repair has been shown to result in functional improvement in patients with secondary MR and HF, a clear survival benefit has not yet been shown. Several ongoing trials are underway to evaluate the outcomes of this specific subgroup of patients. Considering the fact that catheter-based techniques are much less invasive, the optimal timing of intervention in patients with HF and secondary MR should be re-evaluated from this point of view. Although valve repair was not superior to replacement for surgical patients with severe ischaemic MR, perhaps transcatheter replacement versus repair and their timing should be revisited in terms of the severity and staging of MR disease and HF. It is conceivable that earlier transcatheter repair might impact the time course of HF, whereas transcatheter mitral replacement may offer more durable results in patients with more advanced HF who have a high risk for MR recurrence after repair. Whether any or both interventions can provide additional (survival, LV reverse remodelling) advantages aside from functional benefits remains to be seen. Although various technologies and concepts are currently being evaluated, significant advances are required for TMVR to become a routine therapy. Advances in device design should minimize the risk of LVOT obstruction and provide secure anchoring in different

native MV anatomies, anatomic sizes and MR diseases. Planning tools and device deployment routes should be further streamlined to provide safe, secure and successful device deployment.

Secondary MR in patients with HF is a new therapeutic frontier. Although much more challenging than the development of transcatheter aortic valve procedures, a significant therapeutic potential for a much larger patient population exists. However, the feasibility, safety and outcomes of these emerging concepts remain to be extensively evaluated in the not too distant future.

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Central image by Patrick J. Lynch, medical illustrator ([https://commons.wikimedia.org/wiki/File:Heart\\_left\\_atrial\\_appendage\\_tee\\_view.jpg](https://commons.wikimedia.org/wiki/File:Heart_left_atrial_appendage_tee_view.jpg)), 'Heart left atrial appendage tee view', added text, <https://creativecommons.org/licenses/by/2.5/legalcode>.

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