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Post-infarct mitral insufficiency: when to resort to reparative surgery, when to the mitral clip

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Severe mitral insufficiency is a feared complication that develops in 10–12% of patients with myocardial infarction and ST elevation. It results from the rupture of the papillary muscle or is secondary to an acute remodelling of the left ventricle in its entirety or of the infarcted region. The mortality of patients with acute clinical onset reaches 50%. The ideal treatment of acute mitral insufficiency is controversial and still a source of debate. Most of these patients are at high surgical risk or inoperable; therefore, they are treated conservatively and have a poor prognosis. In these candidates, percutaneous treatment of insufficiency with percutaneous edge to edge can be considered an alternative.

Clinical case

An 82-year-old woman, symptomatic of dyspnoea for 3 days, is hospitalized from the emergency room. In history: arterial hypertension, type II diabetes mellitus, and chronic renal failure. On physical examination: signs of cardiac and pulmonary congestion, holosystolic murmur on the mitral focus. Shortly after admission, the patient becomes complicated with acute pulmonary oedema. The shock team is activated. The patient is intubated and placed under mechanical ventilation.

The electrocardiogram shows a significant elevation of the ST in the inferior and posterior leads with anomalous Q waves. An echocardiogram demonstrates severe mitral insufficiency (MI) from anterior leaflet flail (A2–A3) from posteromedial papillary muscle rupture, a preserved systolic function (*Figure 1A* and *B*). Coronary angiography demonstrates significant stenosis of a distal branch of the right coronary artery (TIMI III, *Figure 1C*). In consideration of age and comorbidities, a conservative treatment was decided.

The clinical condition of the patient deteriorated quickly requiring the need for inotropic drugs, aortic counterpulsation, and haemodialysis.

Following discussion among the heart team, we proceed to percutaneous treatment of MI with implantation of 2 Mitraclip XTW (Abbott, Santa Clara, USA) in correspondence with the flail with optimal result (*Figure 2A* and *B*). Following the procedure, the patient improves her haemodynamic condition. After 8 days of the procedure, she is weaned from the ventilator and the need for inotropic drugs. The patient is discharged home on the 18th day with an echocardiogram demonstrating a mild MI and a mean transvalvular gradient of 4 mmHg (*Figure 2C*). No hospitalization for heart failure (HF) was necessary during the following 6 months.

Pathophysiology, epidemiology, and incidence

Acute or subacute ischaemic MI develops in the context of a myocardial infarction as a result of rupture of a

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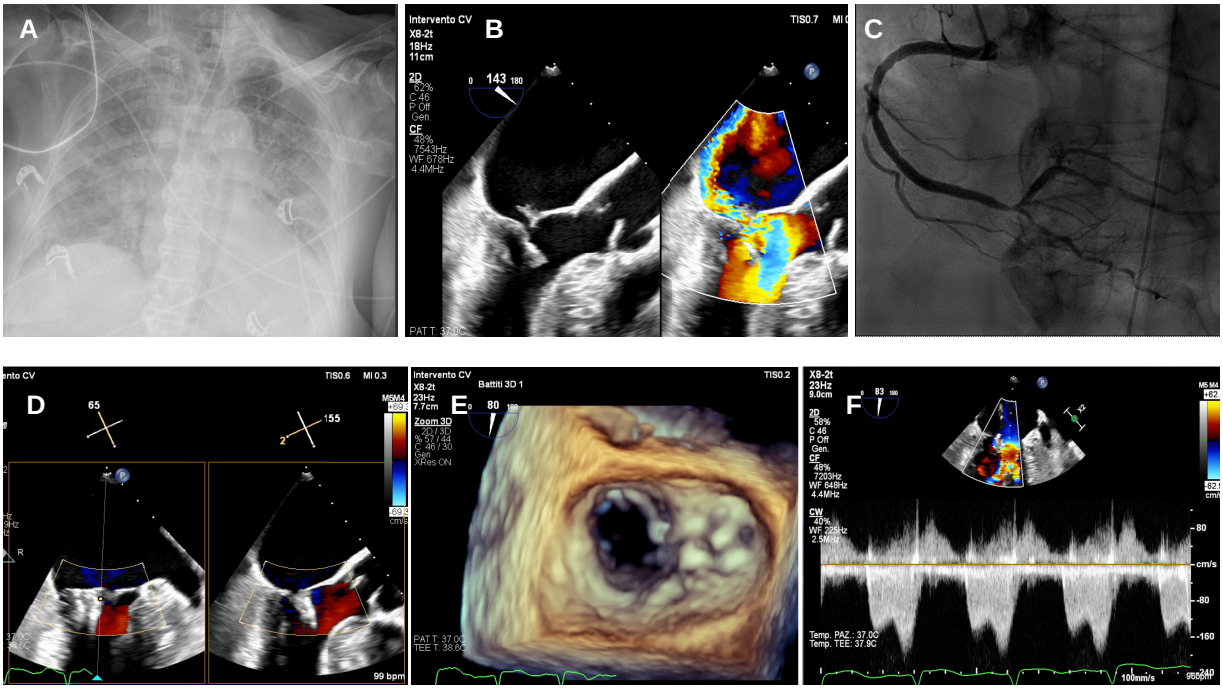

Figure 1 (*A*) Chest X-ray demonstrating acute pulmonary oedema. (*B*) Transesophageal (midesophageal long axis) echocardiography showing posterior mitral flap prolapse due to posteromedial papillary muscle rupture, generating severe eccentric mitral regurgitation (quantitative method). (*C*) Coronary Angiography. Right coronary artery in the left anterior oblique view, showing moderate stenosis in the middle segment and critical lesion in the distal segment with TIMI III flow. IABP positioned in the descending thoracic aorta. (*D* and *E*) 2D transesophageal echocardiography (two midesophageal chambers) and 3D echocardiography, showing the result after percutaneous edge-to-edge mitral valve repair with mild mitral regurgitation. (*F*) Mean mitral gradient after Mitraclip implantation.

papillary muscle or from rapid global or regional ventricular remodelling of the infarcted area that displaces the papillary muscle inferiorly towards the apex and causes tethering of the leaflets and therefore secondary MI.

The most common leaflet dysfunction that occurs during functional MI is Carpentier's type IIIb, with restricted movement of the leaflet in systole. Therefore, in most patients, the diagnosis of ischaemic MI is defined in the context of a previous history of myocardial infarction and predominant posteromedial or posterior leaflet tethering with restricted movement in systole. In a minority of cases, patients present with a type II lesion, with partial or total rupture of the papillary muscle. Complete rupture of a papillary muscle usually leads to an extended flail of both leaflets, while the more common partial rupture involves only part of the leaflet.

Moderate-severe MI is found in 12% of heart attacks with elevated ST at 30 days.[1] The presence of mild MI is also associated with an excess of morbidity and mortality, but the presence of severe moderate MI correlates with the worst outcomes, with a mortality rate of 24, 42, and 52% at 30 days, 6 months, and a year, respectively.[1] The results worsen further if the patient becomes acutely decompensated and requires mechanical ventilation, intravenous inotropics and diuretics and/or mechanical circulatory support.

Most of these patients are at high surgical risk or even inoperable, for a number of reasons: the recent coronary syndrome, haemodynamic instability, and hyper-acute presentation. Until now, the only possible intervention in these cases has been surgical mitral replacement which is associated with a mortality of 25%.[1]

Clinical presentation

Acute MI is often accompanied by haemodynamic instability.[1-3] The relatively acute onset of MI can lead to pulmonary oedema and cardiogenic shock (HF), particularly when it is associated with left ventricular (LV) systolic dysfunction.

The classic pansystolic murmur in the mitral area radiated to the left axillary line is not always present on physical examination. According to some series, in up to half of the patients may be absent. Murmur intensity is usually not related to the degree of regurgitation due to LV dysfunction and left atrium (LA) compliance. Therefore, in the presence of ischaemic cardiomyopathy, the absence of a regurgitation murmur should not rule out the presence of an underlying MI. MI should therefore be excluded in patients who deteriorate rapidly and develop pulmonary oedema immediately after STEMI. Also, once diagnosed, it is important to promptly refer these patients to a tertiary care hospital with a cardiac surgery ward and a shock team.

It is also crucial to carefully evaluate the patient's clinical and haemodynamic status to promptly detect

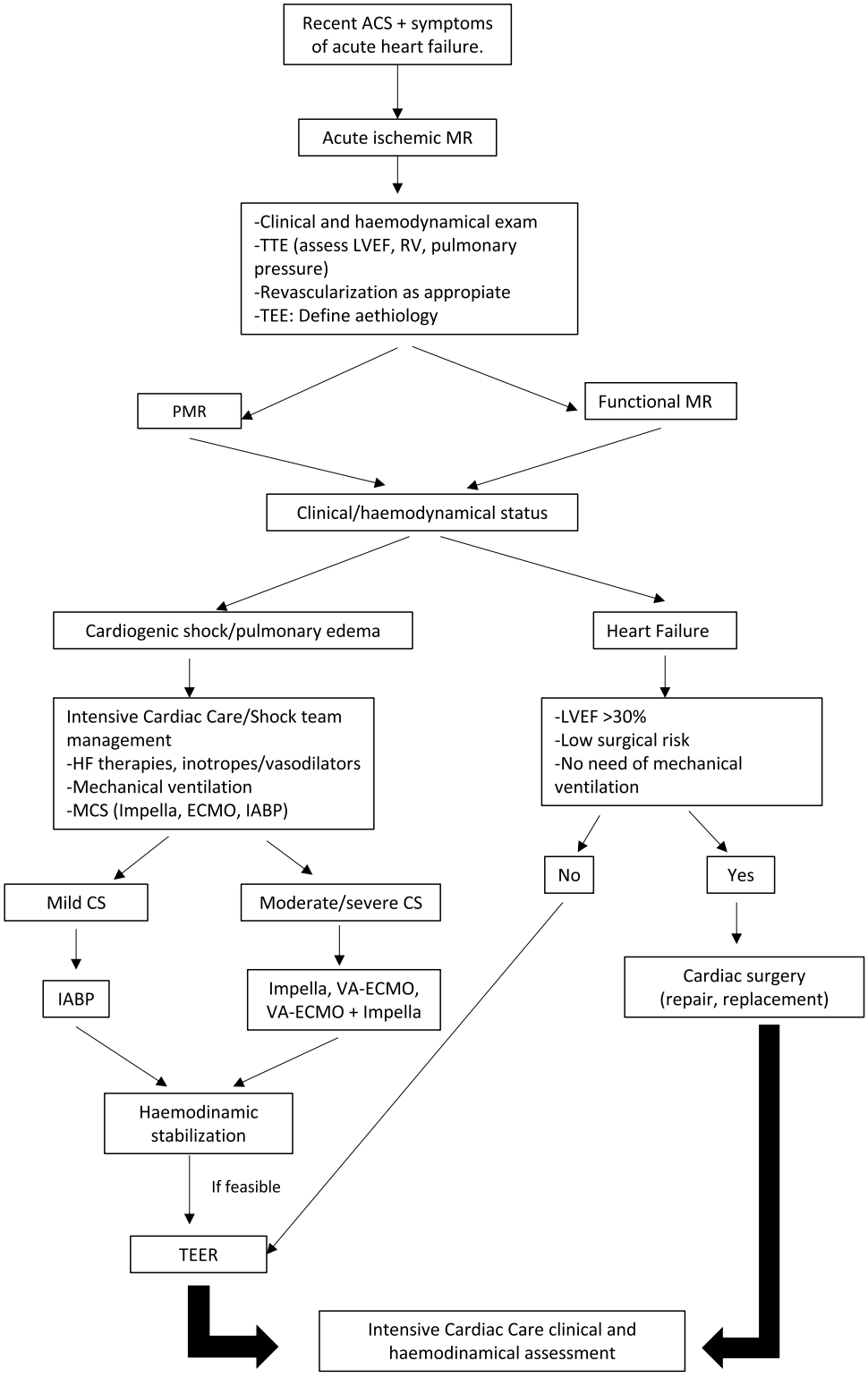

Figure 2 Decision algorithm in patients with post-acute myocardial infarction acute MI. SCA, acute coronary syndrome; MR, mitral regurgitation; AMI, acute myocardial infarction; TTE, transthoracic echocardiography; LVEF, left ventricular ejection fraction; RV, right ventricle; TEE, transesophageal echocardiography; PMR, rupture of the papillary muscle; SC, heart failure; MCS, mechanical circulatory support; ECMO, extracorporeal membrane oxygenation; IABP, aortic contropulsator; TEER, edge-to-edge transcatheter repair.

signs of organ failure and HF. The presence of MI should trigger a sudden reaction of a dedicated team to prepare adequate monitoring of the patient assisting him with aggressive drug therapies and, possibly, with mechanical circulatory support, as shown in *Figure 2*. This multidisciplinary approach must be concerted between cardiac

surgeons, cardiologists, anaesthetists and other specialists involved in acute HF therapy.

Medical therapy aims to reduce MI by reducing afterload with vasodilators, although this is not possible in patients with HF. Aortic contropulsation is the most widely used mechanical support system (MSS) and can be effective alone in non-advanced shock. The use of arteriovenous extracorporeal membrane oxygenation (ECMO) is debated due to the increase in afterload.

Impella (Abiomed), on the other hand, provides the most physiological support for the patient. In a large retrospective study evaluating the use of MSS in patients with papillary muscle rupture from myocardial infarction between 2002 and 2014, the use of MSS remained limited to IABP (91%), ECMO and Impella, were used in 5% and 4.1%[4] of cases respectively, with a high hospital mortality rate (46%). Recently, a retrospective study with a combined strategy between Impella and MitraClip was published that includes HF patients with an 80% survival rate.[5] This new percutaneous management for patients presenting with acute and severe mitral regurgitation complicated by CS should be further investigated in future studies.

Assessment of the extent of ischaemic mitral insufficiency

The main risk in these patients is of missing or underestimated MI because the clinical presentation can be subtle in the absence of a systolic murmur. Therefore, an echocardiogram is mandatory to rule out MI in any patient with unstable conditions in the presence of myocardial infarction. Echocardiography is a key test to quantify the defect, clarify its mechanism, and rule out leaflets abnormalities.[6] Transesophageal echocardiography provides additional information on the mechanism of regurgitation, especially when transthoracic images are not optimal.

The degree of MI can be quantified by the contracted vein, the volume of regurgitation or by the PISA method. The contracted vein calculation is widely used due to its simplicity; however, since the regurgitation orifice in the MI is not circular, its measurement can be misleading. To overcome this limitation and correct the elliptical shape, the average of the contracted vein in two and four chambers is calculated. A mean contracted vein >7 mm is suggestive of severe MI.[6]Alternatively, the volumetric method can be used. In this way, the regurgitation volume is measured as the difference between the mitral and aortic systolic stroke volume.

The flow convergence method is the most recommended quantitative method. The proximal isovelocity surface area (PISA) is measured in the middle of the systole using the first aliasing rate. The effective area of the regurgitation orifice can be calculated using the formula effective regurgitant orifice area (EROA) = $2\ \pi r2V_a/V_p$ where r is the radius of the hemispheric PISA zone, V_a is the aliasing speed and V_p is the IM peak speed. The volume of regurgitation can be calculated as the product of EROA and MR VTI. An EROA greater than 0.2 cm^2, a regurgitation volume ≥30 mL, or a regurgitation fraction ≥50% are indicative of severe MI.[6]

The quantification of MI is also of extreme importance in the management of patients with chronic MI, but in the context of acute MI, the quantification is even more significant, as it can steer the treatment towards a more aggressive gesture in the context of high-risk patients. However, in most cases, the semi-quantitative assessment of the MI and the clinical presentation may be sufficient to make decisions, especially in an emergency. In patients with type III lesions it might be useful to estimate the contractile reserve or the presence of hibernating myocardium in remote areas of ischaemia, but in an emergency it is not feasible from a logistical and clinical point of view.

Surgical treatment as a gold standard

Due to the poor results obtained by conservative approaches, surgery has until recently been the only alternative treatment option in case of post-AMI MI. Comprehensive information on surgical outcomes in this clinical scenario is limited, described only in small case series with an early mortality of approximately 25%.[7]

Current guidelines recommend urgent surgery if the mechanism is papillary muscle rupture, and medical therapies, inotropic support, or mechanical circulatory support are unable to stabilize the patient.[7] However, there is no specific recommendation for acute post-infarct MI.

In the presence of chronic functional MI, the choice of replacement or restorative surgical procedure concomitant or not with myocardial revascularization is debated. The Randomized Ischaemic Mitral Evaluation study showed that adding mitral annuloplasty to coronary artery bypass grafting (CABG) in patients with ischaemic MI improved functional capacity and promoted reverse ventricular remodelling.[8] However, large-scale studies and meta-analyzes have suggested that adding mitral valve repair to CABG did not result in reverse remodelling or clinical benefit.[8]

There are no large studies in the context of acute MI, so most of the information comes from retrospective records.

Lorusso,[9] in a multicentre retrospective registry, evaluated the postoperative outcomes of emergency surgery for severe acute MI in a population of 279 patients. Aetiology included acute myocardial infarction in 126 patients, of whom 52 had severe MI with a type IIIb mechanism. The authors found that early mortality among patients with an ischaemic aetiology was higher than in other aetiologies of acute MI, such as degenerative or infectious endocarditis (26.9% vs. 14.8% and 22.7%, respectively). In addition, postoperative complications were more frequent in patients with acute myocardial infarction, requiring a longer ICU stay, a greater need for inotropes and mechanical support. In this registry, in multivariate analysis, MI, acute endocarditis, LV dysfunction and coronary heart disease were the main predictors of early death.

In post-infarct MI, the impact of coronary revascularization in patients with mitral disease has been

Table 1 Main studies available in the scientific literature to evaluate percutaneous mitral valve repair in patients with acute mitral insufficiency

Authors	Type of study	*N*	Population included	In-hospital mortality	12-month mortality
Haberman *et al.*[14]	Retrospective, comparing conservative, surgical and percutaneous treatment	471	Patients with acute functional post MI MR. Patients with papillary muscle rupture excluded	Surgery 16% Mitraclip 6%	Surgery 31% Mitraclip 17%
Martinez-Gomez *et al.*[12]	Retrospective systematic review	254	Percutaneous mitral valve repair with Mitraclip in unstable patients with cardiogenic shock or acute pulmonary oedema	12.6%	39.1%
Haberman *et al.*[13]	Multinational collaborative data analysis	105	Patients with severe acute RM after MI	8.6%	15.2%

MI, myocardial infarction; MR, mitral regurgitation.

extensively studied. Chevalier *et al.*[10] demonstrated that the absence of myocardial revascularization exerts an additional negative impact on early survival in patients undergoing surgery for post-ischaemic MI.

Since, in the acute setting, repair can be complex and presents a high risk of recurrence, replacement of the mitral valve with preservation or resuspension of the subvalvular apparatus is the technique of choice in most centres.

Edge-to-edge percutaneous mitral plastic surgery: an alternative

Recently, high-volume centres with a previous consolidated experience in the percutaneous edge-to-edge treatment (transcatheter edge to edge repair TEER) of MI have used this technique as an alternative to surgery.

Similar to surgery, there is limited information on the percutaneous treatment of acute ischaemic MI. The data relate to case series and retrospective multi-centre registers.[11] According to these data, TEER treatment after AMI complicated by MI tends to be safer than surgery, but equally effective (*Table 1*).

In most of the reported cases, rescue TEER treatment significantly reduced MI and improved haemodynamic parameters, leading to patient stabilization.[9] However, this series of cases has several limitations that need to be taken into account, include small populations, with retrospective data in the absence of a comparison group. Randomized trials and most real-world registries of TEER treatment have systematically excluded this type of patient, due to the acute clinical context and particularities of the population under consideration.

Martinez-Gomez *et al.*[12] recently reported a systematic review that included a total of 254 unstable patients undergoing TEER for cardiogenic shock or refractory pulmonary oedema with severe acute MI. The most frequent aetiology was ischaemic in 174 patients (68.5%), with acute myocardial infarction in 60.0% of patients. Patients, generally suffering from multiple pathologies, had very high surgical risk scores with a mean Euroscore II of 19.4 [interquartile range (IQR) 15.3-36.5] and an STS of 18.4% (IQR 8.4-23, 9). This study reported procedural success of 93.7%, with an in-hospital mortality rate of 12.6%, which corresponds to an absolute reduction of 7% or 6% in expected mortality according to Euroscore II and STS scores, respectively.

Haberman *et al.*[13] published a multicentre study, which retrospectively included 105 patients with acute and subacute MI, onset in the first 90 days after AMI and treated with MitraClip. Clinical presentation was cardiogenic shock in 57% of cases. Only six patients had MI due to papillary muscle rupture; functional MI without rupture was the most common aetiology in the remaining subjects. In nearly 90% of the total population, the MitraClip rescue procedure significantly reduced MI, as well as pulmonary hypertension and left atrial V wave.

A large cohort of patients with acute myocardial infarction complicated by severe MI undergoing various therapeutic strategies (including surgery and interventional treatment) has recently been published.[14] An overall population of 471 patients (excluding those with papillary muscle rupture) was studied and divided into three cohorts: patients treated conservatively, surgically, or with percutaneous mitral valve repair.

A total of 106 patients were surgically treated and 99 were treated with TEER. The latter were older (71 ± 10 vs. 68 ± 10, $P = 0.03$), had a higher prevalence of previous cardiac events, had history of previous myocardial infarction (56% vs. 14%, $P < 0.01$), and had previous CABG (27% vs. 1%, $P < 0.01$), compared with patients undergoing surgery. Furthermore, patients treated with TEER were more likely to present in severe clinical conditions; 52% of them experienced cardiogenic shock, compared with 31% in the surgical group ($P < 0.01$). It is important to emphasize that (and potentially introducing a selection bias) the interval from AMI to mitral surgery was longer in patients undergoing TEER.

The authors found that patients undergoing surgery (surgical or TEER) had lower in-hospital and 1-year mortality than those treated conservatively.[12] When comparing surgery with percutaneous post-AMI acute MI repair, procedural success does not differ, but in-hospital mortality is significantly higher in surgical patients than in TEER-treated patients (16% vs. 6%, $P < 0.01$). The

difference in mortality between the groups was also consistent at the 1-year follow-up (31% vs. 17%, $P = 0.04$). In Cox regression analysis, surgery was associated with a higher mortality risk than TEER (crude HR 2.45, 95% CI 1.09–5.50, $P = 0.03$; adjusted HR 3.75, 95% CI 1.55–9.07, $P < 0.01$).

These results confirm that TEER treatment is safe and effective in an acute setting for a select group of high-risk patients, who frequently develop cardiogenic shock and present in an unstable condition. Larger, multicentre, randomized studies are needed to confirm these findings.

The main challenge for wider adoption of the transcatheter strategy is the limited availability of therapy; few centres have developed sufficient expertise to manage haemodynamically unstable patients with complex anatomies, particularly in the presence of papillary muscle rupture. Even in highly experienced centres, the availability of a 24-hour emergency TEER service is rare. However, the evidence of favourable outcomes in the literature could lead to the creation of adequate structures and organizations that respond to emergencies.

Is there a place for percutaneous replacement in acute MI?

Transcatheter mitral valve replacement (TMVR) has been mainly evaluated for patients unsuitable for traditional cardiac surgery due to the high surgical risk, combined with complex mitral anatomy for repair techniques (extended calcification of the mitral annulus) or failure of previous mitral valve repair or surgical replacement. To date, there is no evidence that TMVR has been applied in patients in the setting of acute MI. The main limitation is that TMVR requires pre-implantation screening which includes a standardized imaging set and takes time to acquire. Many patients are not anatomically suitable, as most procedures are performed in clinical trials that specifically exclude unstable patients.

In the future, as replacement is the preferred strategy in surgical patients with ischaemic MI due to its predictability and efficacy, it can be expected that TMVR could become an important alternative to TEER in patients with complex anatomy. Currently the only clinically available valve is the Tendyne valve (Abbott, Santa Clara, USA), a transapical device.

Recently, Muller *et al.*[15] published the 2-year follow-up of the first 100 patients enrolled in the Expanded Clinical Study of the Tendyne Mitral Valve System. These patients had symptomatic severe MI (89% secondary) and 66% were NYHA functional class III or IV, with 97% device success and 39% 2-year all-cause mortality (17 of 39 deaths occurred during the first 90 days after the procedure).

Again, in the aforementioned studies, transcatheter mitral valve replacement procedures were performed in an extremely different clinical setting than the acute setting of post-AMI MI. Therefore the results may not be applicable to the acute setting.

Conclusions

Despite optimal medical treatment, patients with acute mitral regurgitation post-AMI frequently develop an unstable clinical situation with a very high mortality rate. In these severely decompensated patients, surgery is often prohibitive. In these high-risk surgical patients, alternative therapies, including mechanical support and percutaneous mitral valve repair, are an attractive option that had shown promise. Large, multicentre, randomized studies are needed to confirm this possibility among patients with acute ischaemic functional MI.

Conflict of interest: None declared.

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