ORIGINAL ARTICLE

# Changes in the Degree of Mitral Regurgitation in Patients with Multiple Valve Disease and Transcatheter Aortic Valve Implantation

## *Cambios en el grado de insuficiencia mitral en pacientes con enfermedad bivalvular e implante valvular aórtico percutáneo*

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## ABSTRACT

**Background:** Patients undergoing double valve replacement due to severe aortic stenosis and significant mitral regurgitation present high surgical morbidity and mortality. It has been suggested that transcatheter aortic valve implantation produces an inverse left ventricular remodeling resulting in favorable changes in the loading conditions and subsequent mitral regurgitation improvement.
**Objective:** The aim of this study was to assess the benefit of isolated transcatheter aortic valve implantation in these patients and to analyze the influence of decreased afterload and favorable left ventricular remodeling on mitral regurgitation.
**Methods:** The study retrospectively analyzed 89 consecutive patients undergoing transcatheter aortic valve implantation at a single center between March 2009 and August 2015, due to symptomatic severe aortic stenosis and high surgical risk. Echocardiograms were analyzed before the procedure and at one-month of follow-up. Forty patients identified with significant mitral regurgitation constituted the final sample and object of this investigation.
**Results:** Baseline mitral regurgitation was classified as severe (+4) in 5 patients (12.5%), moderate to severe (+3) in 18 patients (45%) and mild to moderate (+2) in 17 patients (42.5%). During follow-up, mitral regurgitation was identified as +4 in 1 patient (2.5%), +3 in 12 patients (30 %), +2 in 8 patients (20%), +1 in 15 patients (37.5%) and 4 patients (10%) exhibited no mitral regurgitation; all changes were statistically significant (p=0.045).
**Conclusion:** Our results suggest that in patients with multiple valve disease, rejected for surgical treatment due to high risk, transcatheter aortic valve implantation could be the main therapeutic option, as there is a high probability of mitral regurgitation reduction after the procedure.

**Key words:** Aortic valve - Aortic Stenosis - Mitral Valve Insufficiency - Transcatheter Aortic Valve Implantation

## RESUMEN

**Introducción:** Es conocida la morbimortalidad quirúrgica en pacientes sometidos a doble reemplazo valvular por presentar estenosis aórtica grave e insuficiencia mitral significativa. Se ha sugerido que con posterioridad al reemplazo valvular aórtico percutáneo se produce una remodelación ventricular izquierda inversa con cambios favorables en las condiciones de carga y consecuente mejoría de la insuficiencia mitral.
**Objetivo:** Evaluar el beneficio del reemplazo valvular aórtico percutáneo aislado en dichos pacientes y analizar la influencia de la disminución de la poscarga y la remodelación favorable del ventrículo izquierdo sobre la insuficiencia mitral.
**Material y métodos:** Se evaluaron retrospectivamente 89 pacientes consecutivos de un único centro, sometidos a reemplazo valvular aórtico percutáneo entre marzo de 2009 y agosto de 2015, por presentar estenosis aórtica grave sintomática y riesgo quirúrgico alto. Se analizaron los ecocardiogramas antes del procedimiento y posteriormente al mes de seguimiento. Se identificaron 40 pacientes con insuficiencia mitral significativa, que corresponden a la muestra final y objeto de nuestra investigación.
**Resultados:** La gravedad de la insuficiencia mitral basalmente se clasificó en grave (+4) en 5 pacientes (12,5%), moderada a grave (+3) en 18 (45%) y leve a moderada (+2) en 17 (42,5%). En el seguimiento se identificó insuficiencia mitral +4 en 1 paciente (2,5%), +3 en 12 pacientes (30%), +2 en 8 pacientes (20%), leve (+1) en 15 pacientes (37,5%) y sin insuficiencia en 4 pacientes (10%), siendo estos cambios estadísticamente significativos (p = 0,045).
**Conclusión:** Nuestros resultados sugieren que en los pacientes con enfermedad bivalvular, descartados de tratamiento quirúrgico por riesgo alto, el reemplazo valvular aórtico percutáneo podría ser la principal opción terapéutica, dado que habría una alta probabilidad de que la insuficiencia mitral se reduzca luego del procedimiento.

**Palabras clave:** Válvula aórtica - Estenosis aórtica - Insuficiencia de la válvula mitral - Reemplazo de la válvula aórtica transcatéter

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## Abbreviations

| | | | |
|---|---|---|---|
| **AS** | Aortic stenosis | **TAVI** | Transcatheter aortic valve implantation |
| **MR** | Mitral regurgitation | | |

## INTRODUCTION

Aortic stenosis (AS) is the heart valve disease that most frequently requires surgical or percutaneous treatment. (1, 2) Its association with severe mitral regurgitation (MR) has been reported in 3% to 74% of cases among patients needing either surgical or percutaneous aortic valve treatment. When severe AS coexists with significant MR (≥2), there is an important increase in morbidity and mortality, especially in elderly patients, who should be surgically treated with double valve replacement. (3-5)

A recent meta-analysis demonstrated that the presence of significant MR (moderate to severe) could increase both early and late mortality after aortic valve replacement, suggesting that double valve replacement should be performed, regardless of the degree of MR (moderate, moderate to severe or severe). (6)

There is a certain controversy with respect to MR classified as less than severe, with very limited bibliography about the series of patients with untreated moderate MR after aortic valve replacement. Today, most researchers and highly renowned surgical teams suggest its replacement, too. (7)

Several studies have identified the concomitant presence of moderate to severe MR as an independent predictor of mid-term mortality in patients with high risk AS undergoing transcatheter aortic valve implantation (TAVI). German and Italian registries showed that the presence of at least mild to moderate MR (+2) is a strong predictor of mortality at one year and this prognosis was established as of one month after the procedure. (8)

Changes in MR after TAVI were reported in several studies, some with interesting and positive results. In these studies, between 17% and 22% of patients improved previously significant MR after TAVI, while 11% to 22% of cases worsened their MR. The specific predictors of this improvement have not been well established. (8)

Chronic increased afterload, concentric hypertrophy and increased transmitral gradients produced by AS could impair a previously existing structural MR or produce MR in a formerly healthy valve without demonstrable structural anomalies. The progression to diastolic dysfunction and the concomitant systolic volume could even worsen mitral valve dysfunction. (7) Numerous studies have suggested that after TAVI, an inverse left ventricular remodeling is produced with favorable changes in the loading conditions; consequently MR could improve after isolated aortic valve replacement in patients with multiple valve disease (3, 4, 9)

The aim of the present study was thus to analyze the changes in the severity of MR in high surgical risk patients with severe AS and moderate or severe MR undergoing TAVI.

## METHODS

A retrospective study was performed using the Interventional Cardiology laboratory database of a single center in Buenos Aires, the Instituto de Cardiología y Cirugía Cardiovascular Fundación Favaloro. Between March 2009 and August 2015, 156 patients underwent TAVI with the CoreValve reValving CoreValve™ System (Medtronic, CoreValve, Minneapolis, Minnesota), due to severe AS and high surgical risk assessed by the Heart Team of the same center. Among the 156 patients, those with echocardiographic studies in the Favaloro Foundation Echocardiography and Vascular Doppler laboratory, both prior to the procedures as in the first month post-TAVI and in the follow-up period beyond the initial 30 days, were selected, resulting in a total of 89 patients who completed follow-up. In addition, patients with significant MR (≥2) were identified, with a total of 40 patients corresponding to the total sample and purpose of our study (Figure 1).

Clinical data obtained from the computerized clinical records, such as age, gender, weight, height, body surface area and presence of risk factors, as hypertension, diabetes mellitus, dyslipidemia and smoking were collected. Also, history of ischemic heart disease and presence of significant coronary lesions were identified (Table 1).

Ventricular diameters, valve areas, estimated ejection fraction, thorough assessment of both valves, aortic valve area, gradients and velocities (pre- and post-procedure), concomitant aortic regurgitation (prior or periprosthesic leaks), evaluation of mitral anatomy, annular dilatation, prior structural damage, presence of calcium, fibrosis or mitral single or bi-leaflet prolapse, quantification of insufficiency by qualitative, semi-quantitative and quantitative methods (effective regurgitant orifice, vena contracta, regurgitant volume and operator subjective assessment) were obtained from the Echocardiography and Vascular Doppler laboratory database. Mitral regurgitation was graded according to the classification proposed by the ASE guidelines, as severe (+4), moderate to severe (+3), mild to moderate (+2) and mild (+1).

### Statistical analysis

Continuous variables were analyzed using mean, median and standard deviation and two-sample t test, while variables with non-Gaussian distribution were analyzed with the Wilcoxon test. Categorical qualitative variables were analyzed using frequency, percentages and the chi-square or Fisher's exact tests. IBM SPSS version 20 software for Argentina was used to perform analyses. Statistical significance was established for $p < 0.05$.

### Ethical considerations

The research study was performed according to ethical considerations, keeping absolute confidentiality of the collected data, which were only used with the aim of completing this

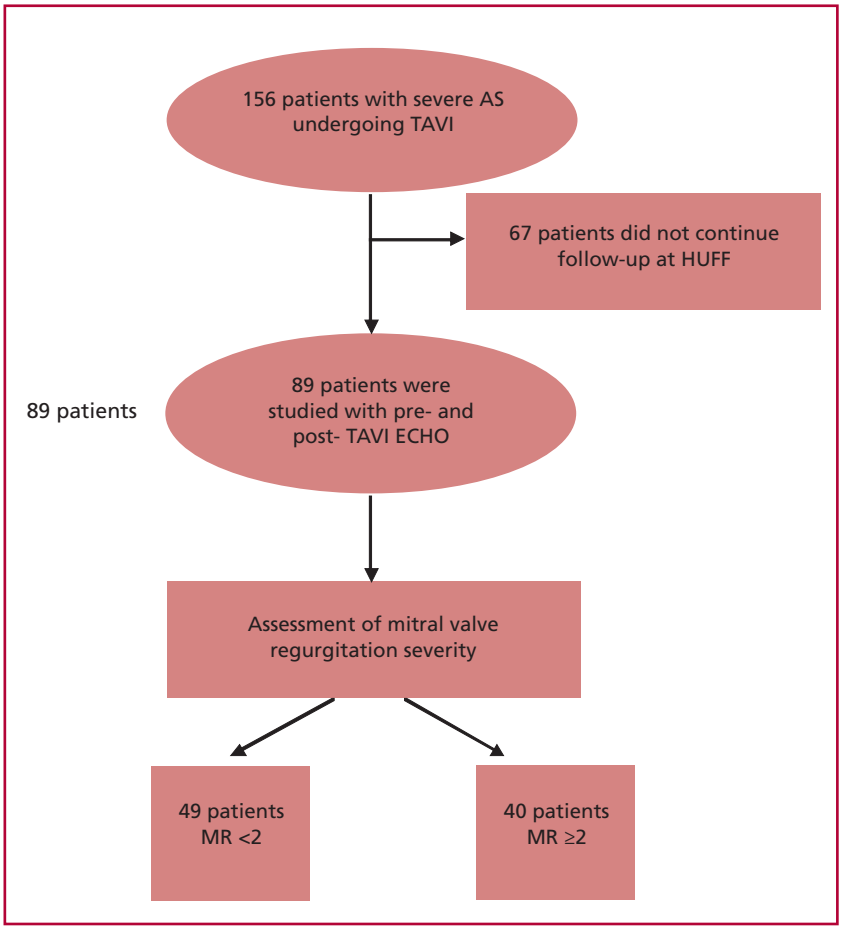


**Fig. 1.** Population sampling. Among 156 consecutive patients undergoing TAVI, only 89 patients could be studied in our echocardiography laboratory. From this sample, 49 patients (55 %) presented <2 (absent or mild) degrees of mitral valve regurgitation and 40 patients (45%) presented with ≥2 (mild to moderate, moderate to severe and severe) degrees of mitral valve regurgitation. AS: Aortic stenosis. HUFF: Hospital Universitario Fundación Favaloro. ECHO: Echocardiography.

work and for no other purpose. The investigator was responsible of ensuring adequate quality of the information obtained through the Echocardiography and Vascular Doppler Unit database and the computerized clinical records.

## RESULTS

Among the cohort of 89 patients who completed follow-up, 40 (44.9%) presented a significant degree of MR (≥2): +4 in 5 patients (12.5%), +3 in 18 patients (45%) and +2 in 17 patients (42.5%). Among them, 27 patients (67.5%) presented some degree of abnormal valve structure, as myxomatous degeneration, leaflet or annulus calcification, or valve fibrosis and were reported as of organic or mixed etiology, and the other 13 patients (32.5%) had MR identified as of functional origin. Ischemic MR was determined based on the presence of significant coronary lesions and altered wall motility, resulting in abnormal leaflet coaptation. None of them presented signs of rheumatic aggression or leaflet prolapse.

Mean population age was 79±7.5 years, with a similar distribution among sexes (47.5% were men).

The echocardiography performed more than 30 days after the procedure identified severe MR (+4) in 1 patient (2.5%), moderate to severe (+3) in 12 patients (30%), moderate (+2) in 8 patients (20%), mild (+1) in 15 patients (37.5%) and 4 patients without regurgitation (10%); these changes were statistically significant (p=0.045) (Table 2).

The reduction of valve regurgitation was evident in 27 patients (67.5%): 1 grade in 16 patients (40%), 2 grades in 10 patients (25%) and 3 grades in 1 patient (2.5%). Eleven patients (27.5%) did not show any changes and only 2 patients (5%) evidenced worse MR severity, which increased one grade (from mild to moderate to moderate to severe) (Figure 2).

No significant differences were found in left ventricular ejection fraction. (50.2±14.8 % vs. 54.4±11.5 %; p=0.3), pulmonary artery systolic pressure (45.8±12.4 mmHg vs. 43±12.5 mmHg; p=0.2), or between pre-and postprocedural organic or functional etiology. Conversely, significant changes were observed in ventricular systolic (52.5±8 mm vs. 48.8±7.1 mm; p=0.003) and diastolic (35.4±10.3 mm vs. 31.4±8.6 mm; p=0.006) diameters, left ventricular mass index (138±38.9 g/m2 vs. 117.1±33.8 g/m2; p=0.003), maximum aortic velocity (4.4±0.9 cm2 vs. 2.05±0.6 cm2; p <0.0001) and aortic gradients (maximum gradient: 82.4±32.2 mmHg vs. 18.9±11.4 mmHg; p <0.0001 and mean gradient: 50±23.4 mmHg vs. 10.3±6.5 mmHg, p <0.0001) (see Table 2).

None of the patients in the selected group with

**Table 1.** Patient baseline characteristics

| | Total n=40 |
|---|---|
| Age, mean±SD | 79±7.5 |
| Male gender, n (%) | 19 (47.5) |
| Weight, kg | 77.90±17.4 |
| Height, cm | 164.8±10.3 |
| Body surface area, m2 | 1.96±0.2 |
| Risk factors | |
| Hypertension, n (%) | 27 (67.5) |
| Dyslipidemia, n (%) | 13 (32.5) |
| Diabetes mellitus, n (%) | 8 (20) |
| Smoking, n (%) | 12 (30) |
| Associated ischemic heart disease | |
| Prior acute myocardial infarction, n (%) | 4 (10) |
| Severe LMCA stenosis, n (%) | 1 (2.5) |
| Severe ADA stenosis, n (%) | 18 (45) |
| Severe LCX stenosis, n (%) | 5 (12.5) |
| Severe RCA stenosis, n (%) | 17 (42.5) |
| Prior coronary artery bypass graft surgery, n (%) | 6 (15) |
| Echocardiographic parameters | |
| Left ventricular diastolic diameter, mm | 52.5±8 |
| Left ventricular systolic diameter, mm | 35.4±10.3 |
| Ejection fraction, % | 50.2±14.8 |
| Left ventricular mass index, g/m2 | 139.1±38.9 |
| Left atrial area, cm2 | 28.8±6.7 |
| Aortic valve area, cm2 | 0.6±0.2 |
| Maximum aortic velocity, m/s | 4.4±0.9 |
| Maximum aortic gradient, mmHg | 82.4±32.2 |
| Mean aortic gradient, mmHg | 49.9±23.4 |
| Aortic regurgitation, n (%) | 34 (85) |
| None | 6 (15 ) |
| Mild/Mild to moderate | 21 (52.5) |
| Moderate/Moderate to severe | 13 (32.5) |
| Severe | 0 |
| Mitral regurgitation etiology | |
| Functional, n (%) | 13 (32.5) |
| Organic, n (%) | 27 (67.5) |
| Mitral regurgitation grading (≥ 2), n | 40 |
| Mild to moderate (+2), n (%) | 17 (42.5) |
| Moderate to severe (+3), n (%) | 18 (54) |
| Severe (+4), n (%) | 5 (12.5) |
| Pulmonary artery systolic pressure, mmHg | 45.8±12.4 |

SD: Standard deviation. LMCA: Left main coronary artery. ADA: Anterior descending artery. LCX: Left circumflex artery. RCA: Right coronary artery.

significant MR died in the long-term follow-up. The incidence of postprocedural complications, including stroke, vascular complications and infective endocarditis was almost irrelevant.

## DISCUSSION

This is the first study performed in our country evaluating the decrease in the degree of MR in patients undergoing TAVI due to AS. In our population of patients with severe AS with indication of transcatheter valve implantation, we found a high prevalence of significant MR (44.9%), which has negative implications in postprocedural patient prognosis and survival.

The prevalence of severe MR in patients undergoing TAVI has been described since the PARTNER registries, with an incidence between 2% and 33%. However, trials as the PARTNER A, B and Canadian studies used the Edwards SAPIEN™ transcatheter heart valve system. Italian registries published data using the CoreValve™ system, as French, German, Spanish and other European countries which used both systems (CoreValve™ type and Edwards SAPI-

**Table 2.** Univariate analysis comparing pre- and post-TAVI echocardiographic parameters

| | Pre-TAVI | Post-TAVI | p |
|---|---|---|---|
| Left ventricular diastolic diameter, mm | 52.5±8 | 48.8±7.1 | **0.003** |
| Left ventricular systolic diameter, mm | 35.4±10.3 | 31.4±8.6 | **0.006** |
| Ejection fraction, % | 50.2±14.8 | 52.3±11.4 | 0.3 |
| Left ventricular mass index, g/m2 | 139.1±38.9 | 117.1±33.8 | 0.003 |
| Maximum aortic velocity, m/s | 4.4±0.9 | 2.05±0.6 | **<0.0001** |
| Maximum aortic gradient, mmHg | 82.4±32.2 | 18.9±11.4 | **<0.0001** |
| Mean aortic gradient, mmHg | 49.9±23.4 | 10.3±6.5 | **<0.0001** |
| Aortic regurgitation, n (%) | 34 (85) | 29 (72.5) | 0.7 |
| None | 6 (15 ) | 11 (27.5) | |
| Mild/Mild to moderate | 21 (52.5) | 23 (57.5) | |
| Moderate/Moderate to severe | 13 (32.5) | 5 (12.5) | |
| Severe | 0 | 1 (2.5) | |
| Mitral regurgitation | **40** | **21** | **<0.045** |
| None (0) | 0 | 4 (10) | |
| Mild (+1) | 0 | 15 (37.5) | |
| Mild to moderate (+2) | 17 (42.5) | 8 (20) | |
| Moderate to severe (+3) | 18 (54) | 12 (30) | |
| Severe (+4) | 5 (12.5) | 1 (2.5) | |
| Pulmonary artery systolic pressure, mmHg | 45.8±12.4 | 43.0±12.5 | 0.2 |

TAVI: Transcatheter aortic valve implantation

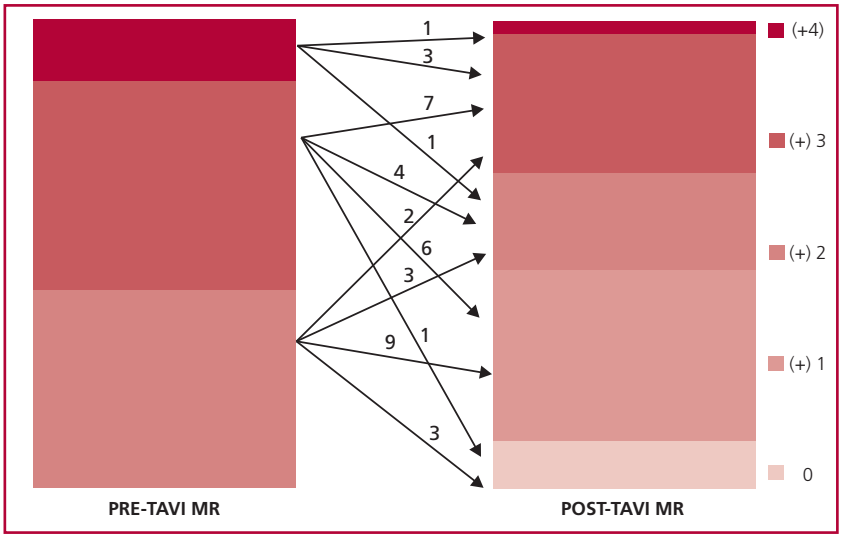


**Fig. 2.** Changes in the degree of mitral valve regurgitation in post-transcatheter aortic valve implantation (TAVI) patients. The left bar shows the group of 40 patients with significant mitral regurgitation (MR) (≥2) prior to TAVI: 5 patients presenting with grade +4, 18 patients grade +3 and 17 with grade +2. The right bar shows that among the 5 patients with severe mitral regurgitation, 1 remained without changes, 3 improved 1 grade the regurgitation and 1 improved 2 grades after the procedure. Among the 18 patients with moderate/severe mitral regurgitation, 7 remained without changes, 4 improved 1 grade, 6 improved 2 grades and 1 improved 3 grades. Among the the 17 patients with mild to moderate mitral regurgitation, 2 worsened the regurgitation, 3 remained without changes, 9 improved 1 grade and 3 improved 2 grades.

EN™ type). Moreover, MR was classified in 4 grades in some studies and in 3 in others (mild, moderate and severe) hampering an even distribution of severity. However, grade ≥2 systematically refers to moderate/severe in all cases. (10-19) Among studies identifying grades ≥2 as significant regurgitation, there is coincidence in the improvement of MR after valve replacement. (19-23)

Improvement of MR after surgical aortic valve replacement has been evaluated in two prospective studies. Tassan-Mangina et al. analyzed 23 patients with functional MR and found improvement in 61% of cases. (20) Similarly, Unger et al. conducted a study with 58 patients with organic or functional MR and observed a decrease in the effective regurgitant orifice area in 69% of patients. (9) In this line of study, Giordana et al. evaluated 35 patients with significant MR (≥2) undergoing TAVI (Edwards SAPIEN™ and CoreValve™) targeting a significant decrease in the post-TAVI degree of MR severity (+2.5 pre-TAVI vs. +1.3 post-TAVI); however, when a subgroup analysis was performed, the improvement in MR was only observed in patients receiving an Edwards SAPIEN™ valve. (22)

Mitral regurgitation severity results from a complex interaction between causal mechanisms, the effective regurgitant orifice area, its dynamic behavior during the cardiac cycle and the magnitude of pres-

sure gradients between the left ventricle and the left atrium. In patients with AS undergoing TAVI, numerous physiological changes take place that might explain the short- and long-term reduction of MR. The drop in left ventricular pressure after TAVI would consequently reduce pressure and transmitral gradient, resulting in a reduction of the degree of MR in the immediate post-procedural period. In some patients with functional MR, the drop in transmitral gradient could lead to a reduction of the closing forces, with MR remaining similar to that before valve replacement. Conversely, the reversion of hypertrophy due to the fall in ventricular afterload would produce an inverse remodeling with changes in ventricular geometry which might contribute to the decrease of MR secondary to the reduction of ventricular end-diastolic volume and tethering forces, mechanism implicated in the long-term changes of MR. This could explain why in most studies on this topic, the patients who most benefited from aortic valve replacement were of organic origin.

The presence of functional MR has been associated as one of the most important factors for post-TAVI improvement in severity, as demonstrated by Toggeweiler et al. who found in a multivariate analysis that functional MR, mean transaortic gradient >40 mmHg, absence of pulmonary hypertension and of AF were independent predictors of MR improvement. (23)

Surgical decision making for double valve replacement is currently a challenge in patients with severe multiple valve disease (AS and MR), especially in those with high risk criteria (according to EuroSCORE and STS). (24-27)

In turn, the present results demonstrate that an adequately thorough echocardiographic assessment is essential both before as after the procedure to predict adverse outcomes (Figure 3).

Additional larger studies would be necessary to establish the clinical and echocardiographic predictors of regurgitation improvement and their correlation with survival after treatment.

### Limitations

This is a retrospective study in a small population of patients undergoing TAVI in a single center. It should be pointed out that when pre- and-post-procedural studies were required, those patients who were not authorized to have the echocardiographic study at Fundación Favaloro (67 patients) were lost to follow-up and hence removed from the analysis, with unknown outcome.

## CONCLUSION

The results show that in patients with multiple valve disease, such as severe AS and significant MR, excluded from surgical treatment due to high perioperative risk, isolated TAVI could be the initial therapeutic choice, considering that there is high probability that MR will improve after the procedure. It is still unknown which are the causes or variables associated with this improvement.

### Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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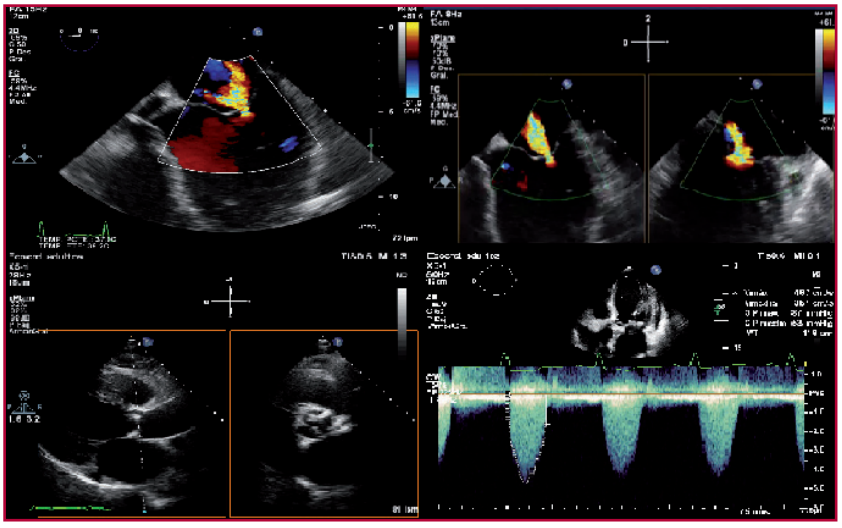

**Fig. 3.** Transthoracic and transesophageal echocardiogram of a patient with severe aortic stenosis and severe mitral regurgitation in the pre-transcatheter aortic valve implantation assessment. The upper images show mitral valve regurgitation severity evaluated through the estimation of the effective regurgitant orifice area (2D transesophageal echocardiography, left image) and biplanar assessment (X-plane type) to estimate the orifice in 3D (right image). The lower images show aortic stenosis assessment through estimation of the outflow tract diameter, the area by planimetry (left) and estimation of the area by the continuity equation using maximum velocity obtained with continuous Doppler.

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