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# Association of tricuspid regurgitation with clinical and echocardiographic outcomes after percutaneous mitral valve repair with the MitraClip System: 30-day and 12-month follow-up from the GRASP Registry

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**Aim** The aim of this study was to evaluate the association of baseline tricuspid regurgitation (TR) on the outcomes after percutaneous mitral valve repair (PMVR) with the MitraClip system.

**Methods and results** Data from 146 consecutive patients with functional mitral regurgitation (MR) were obtained. Two different groups, dichotomized according to the degree of pre-procedural TR (moderate/severe, $n = 47$ and none/mild, $n = 99$), had their clinical and echocardiographic outcomes through 12-month compared. At 30-day, the primary safety endpoint was significantly higher in moderate/severe TR compared with none/mild TR (10.6 vs. 2.0%, $P = 0.035$). Marked reduction in MR grades observed post-procedure were maintained through 12 months. Although NYHA functional class significantly improved in both groups compared with baseline, it was impaired in moderate/severe TR compared with the none/mild TR group (NYHA > II at 30 day: 33.3 vs. 9.2%, $P < 0.001$; at 1 year: 38.5 vs. 12.3%, respectively, $P = 0.006$). Left ventricle reverse remodelling and ejection fraction improvement were revealed in both groups. The primary efficacy endpoint at 12-month determined by freedom from death, surgery for mitral valve dysfunction, or grade ≥3+ MR was comparable between groups, but combined death and re-hospitalization for heart failure rates were higher in the moderate/severe TR group. Multivariable Cox regression analysis demonstrated that baseline moderate/severe TR and chronic kidney disease were independent predictors of this combined endpoint.

**Conclusions** Although PMVR with MitraClip led to improvement in MR, TR, and NYHA functional class in patients with baseline moderate/severe TR, the primary safety endpoint at 30-day was impaired, while moderate/severe TR independently predicted death and re-hospitalization for heart failure at 12-month.

**Keywords** Mitral regurgitation • Percutaneous mitral valve repair • Tricuspid regurgitation • MitraClip

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# Introduction

Severe mitral regurgitation (MR) is associated with progressive left ventricular (LV) dysfunction and congestive heart failure (HF) leading to high rates of morbidity and mortality.[1,2] Current guidelines recommend surgery for moderate-to-severe (3+) or severe (4+) MR in patients with symptoms or evidence of LV dysfunction;[3] however, when MR is secondary to underlying LV dysfunction [i.e. functional MR (FMR)], the benefit for surgery is controversial;[4] therefore, patients with FMR and high-surgical risk are frequently denied surgery and referred to isolated clinical management, carrying poor long-term prognosis.[5]

Recently, percutaneous mitral valve repair (PMVR) with the MitraClip system (Abbott Vascular, Abbott Park, IL, USA) emerged as a safe, less invasive, therapeutic option in patients with 3+ or 4+ MR associated with high-surgical risk;[6] this novel therapy is associated with efficacious MR reduction, improvement in congestive HF symptoms, as well as left ventricle reverse remodelling.[7–9]

Functional tricuspid regurgitation (TR), which occurs on structurally normal tricuspid valves, is frequently observed in patients with MR. The prevalence of moderate/severe functional TR ranges from 8 to 45% in patients undergoing surgical intervention for MR.[10–14] While surgical series of mitral valve repair have demonstrated that the presence of baseline moderate/severe TR negatively impacts on outcomes compared with none/mild TR, the progression of functional TR was identified as a strong predictor of worse outcomes.[15]

The association of pre-procedural TR on clinical outcomes in patients undergoing PMVR with the MitraClip system has not been assessed. In the present study, we sought to evaluate, in consecutive patients with FMR undergoing PMVR with MitraClip in a 'real-world' setting, the association of moderate/severe TR on clinical and echocardiographic outcomes through the 12-month follow-up.

# Methods

## Study population and study design

Patients with symptoms or signs of left ventricle deterioration and 3+ or 4+ MR determined by combined transthoracic and transoesophageal echocardiogram[16–18] considered to be at high-surgical risk by an interdisciplinary team of cardiologists, interventional cardiologists, cardiac surgeons, and anaesthesiologists underwent percutaneous edge-to-edge mitral valve repair with MitraClip at Ferrarotto Hospital, University of Catania, Catania, Italy, from August 2008 to December 2013 as part of the ongoing Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation (GRASP) registry, which results have been partly published elsewhere.[19] After receiving a complete oral and written explanation of the issues surrounding the procedure, all the patients included in the study signed a written consent. The study was approved by the local ethics committee. Qualifying inclusion and exclusion criteria for MitraClip therapy (clinical and echocardiographic), as well as details of the procedure have been previously reported.[7] After excluding the patients with degenerative MR ($n = 25$), we dichotomized our population based on the presence and magnitude of baseline TR, as follows: patients with moderate/severe TR and patients with none/mild TR. Clinical and echocardiographic outcomes were then compared between the two groups. In addition, we assessed the association of TR on outcomes in two groups based on the baseline LVEF (i.e. LVEF $<$ 35% vs. LVEF $\geq$ 35%).[20]

## Echocardiographic assessment

All the patients underwent transthoracic two-dimensional echocardiography at baseline, at hospital discharge, at 30-day, and at 12-month after the procedure. MR and TR severity was graded by the vena contracta (VC) width and the proximal isovelocity surface area method to measure effective regurgitant orifice area (EROA) and regurgitant volume (R Vol) according to the current guidelines.[16–18] MR was considered severe (indicated as 4+) for values of EROA $>$40 mm$^2$ or R Vol $>$ 60 mL; the quantification of mild (indicated as 1+) and moderate was performed using the VC width. Since intermediate values of VC width are not able to discern between mild-to-moderate (indicated as 2+) and moderate-to-severe (indicated as 3+) MR, and guidelines do not indicate cut-off values of EROA and R Vol for these two MR degrees, we graded it combining the values of a qualitative method (colour flow MR jet), semi-quantitative methods (VC width, pulmonary vein flow, and mitral inflow), and quantitative methods (EROA and R Vol). Patients with secondary TR were only included. TR was considered severe for value of EROA $\geq$ 40 mm$^2$ or R Vol $\geq$ 45 mL and for value of VC width $>$ 7 mm. Other parameters such as jet density and contour of continuous wave signal and hepatic vein flow pattern were also utilized for TR grading. The dichotomization into non-significant TR (none/mild) and significant TR (moderate/severe) was chosen to account for inaccuracies due to the semi-quantitative assessment of mild/moderate TR by echocardiography.[20,21] Echocardiographic data were separately analysed by a team of two expert echocardiographers and reviewed by a third reader for consensus when there was disagreement. To determine reproducibility of TR grading assessments, data were analysed by two independent analysts and repeated 1 month after initial analysis.

## Endpoints and follow-up

Acute device success was defined as residual MR $\leq$ 2+ after clip implantation. The primary safety endpoint was the incidence of major adverse events at 30-day, defined as the composite of death, myocardial infarction, reoperation for failed MitraClip implantation, non-elective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for $>$48 h, gastrointestinal complication requiring surgery, new-onset of permanent atrial fibrillation, septicaemia, and transfusion of 2 U of blood. The primary efficacy endpoint was freedom from death, surgery for mitral valve dysfunction, or grade $\geq$ 3+ MR at the 12-month follow-up after clip implantation. Composite endpoint was defined as death or re-hospitalization for HF. Re-hospitalization for HF was defined as new-onset or worsening signs and symptoms of HF which require urgent therapy and result in hospitalization. Clinical follow-up was conducted by clinical visits and/or phone consultation at 30-day, 6-month, and 12-month, and annually thereafter. The median follow-up was 20 months [inter-quartile range (IQR): 12–34 months), and no patient was lost to follow-up. Any death or re-hospitalization was recorded during the follow-up period.

## Statistical analysis

Continuous variables following a normal distribution are presented as mean $\pm$ SD and were compared using Student's *t*-test. One-way analysis of variance or Jonckheere–Terpstra test was used as appropriate for comparisons across multiple groups and to generate *P*-values for trend tests. Categorical variables are presented as counts and percentages and were compared by the Chi-square or Fisher's exact test. Inter-observer and intra-observer reliability were assessed using Cohen's statistic.[22] Survival curves were generated using the Kaplan–Meier method, and log-rank tests were used to evaluate differences between groups. Prognostic values of baseline moderate/severe TR compared with none/mild TR as the referent were assessed using a Cox regression

hazard model. Cox regression analysis was performed to identify independent predictors of the primary endpoint of 12-month mortality and re-hospitalization after MitraClip, expressed as hazard ratio (HR) and 95% confidence interval (95% CI). Candidates variables for the multivariable model were those considered clinically relevant (i.e. baseline moderate/severe TR, chronic kidney disease, and atrial fibrillation) and with a *P*-value $<0.10$ at the univariate analysis. All *P*-values reported are two-sided, and *P*-values $<0.05$ were considered significant. All data were processed using the Statistical Package for the Social Sciences version 21 (SPSS v21, Inc., Chicago, IL, USA).

# Results

## Baseline characteristics

Baseline characteristics were well balanced between the groups. While the STS score was comparable between the groups, EuroSCORE II was higher in the moderate/severe TR group ($n = 47$) compared with the none/mild TR group ($n = 99$) (*Table 1*). Ejection fraction (EF) and left chambers' sizes were comparable between groups, but the right atrial area and the right ventricle diameter were larger in the moderate/severe TR group compared with the none/mild TR group; in addition, pulmonary artery systolic pressure (PASP) was higher in the former. No differences were revealed in the severity of MR between groups, whereas more severe NYHA functional class was demonstrated in the moderate/severe TR group. We demonstrated low intra- (Cohen kappa $= 0.87$, $P < 0.001$) and inter-observer (Cohen kappa $= 0.80$, $P < 0.001$) variability for TR grading.

## Acute and 30-day outcomes

All the procedures were performed without clip-related complications, such as embolization, cardiac tamponade, or peri-procedural stroke. Marked improvement in MR was demonstrated in both groups (*Figure 1*), leading to high rates of device success (97.9 vs. 99.0%, respectively, $P = 0.542$). The reduction in MR was successfully achieved with the implantation of a single clip/patient in 61.7 and 57.6% of the patients, respectively, for the moderate/severe TR and none/mild TR groups ($P = 0.636$). No significant differences were documented regarding device time, procedure time, and length of hospital stay between the groups. Data were available for 100% of the patients at 30-day follow-up. Higher rates of adverse events were identified in the moderate/severe TR group compared with the none/mild TR group (primary safety endpoint: 10.6 and 2.0%, respectively, $P = 0.035$) (*Table 2*), while the primary efficacy endpoint was comparable between the groups (95.7 and 96.0%, respectively, $P = 0.630$). Furthermore, while the benefits observed in terms of MR reduction were sustained over time in both groups, TR was markedly improved in the moderate/severe TR group, but the between-group differences were maintained (*Table 2*; *Figures 1* and *2*). Although NYHA functional class was improved through 30-day in both groups compared with baseline, patients included in the none/mild TR group were in better functional class compared with the moderate/severe TR group (*Table 2* and *Figure 3*).

## Twelve-month outcomes

Kaplan–Meier freedom from death, surgery for mitral valve dysfunction, or grade $\geq 3+$ MR at 12-month (primary efficacy endpoint) was demonstrated in 74.2 and 85.0% of the patients, respectively, in

**Table 1 Baseline characteristics**

| Variable | Moderate/severe TR ($n = 47$) | None/mild TR ($n = 99$) | *P*-value |
|---|---|---|---|
| Age, year | 73.2 ± 6.4 | 70.8 ± 9.9 | 0.070 |
| Male, *n* (%) | 27 (57.4) | 66 (66.7) | 0.279 |
| Hypertension, *n* (%) | 37 (78.7) | 73 (73.7) | 0.514 |
| Diabetes, *n* (%) | 22 (46.8) | 35 (35.4) | 0.185 |
| Atrial fibrillation, *n* (%) | 22 (46.8) | 34 (34.3) | 0.148 |
| COPD, *n* (%) | 11 (23.4) | 25 (25.3) | 0.809 |
| Previous PCI, *n* (%) | 18 (38.3) | 26 (26.3) | 0.139 |
| Previous cardiac surgery, *n* (%) | 17 (36.2) | 25 (25.3) | 0.173 |
| Chronic kidney disease *n* (%) | 27 (57.4) | 47 (47.5) | 0.260 |
| Prior myocardial infarction, *n* (%) | 20 (42.6) | 37 (37.4) | 0.549 |
| Prior stroke, *n* (%) | 6 (12.8) | 6 (6.1) | 0.168 |
| EuroSCORE II, % | 9.3 ± 5.7 | 7.1 ± 5.9 | 0.042 |
| STS score mortality, % | 7.9 ± 7.8 | 6.4 ± 7.1 | 0.260 |
| LVEF, % | 31.7 ± 10.5 | 34.0 ± 11.5 | 0.260 |
| LVEDV, mL | 168.5 ± 55.9 | 175.6 ± 79.5 | 0.539 |
| LVESV, mL | 117.9 ± 53.8 | 120.1 ± 71.3 | 0.854 |
| LVEDD, mm | 60.5 ± 8.3 | 62.0 ± 11.7 | 0.375 |
| LVESD, mm | 45.4 ± 10.9 | 47.1 ± 13.7 | 0.472 |
| Left atrial volume, mL | 105.5 ± 31.4 | 96.2 ± 46.3 | 0.214 |
| Mitral valve area, $cm^2$ | 4.23 ± 0.82 | 4.02 ± 0.78 | 0.138 |
| Mitral valve gradient, mmHg | 1.90 ± 0.90 | 1.91 ± 0.92 | 0.946 |
| Right atrial area, $cm^2$ | 21.1 ± 6.6 | 18.4 ± 4.7 | 0.015 |
| Right ventricle diameter, mm | 33.6 ± 6.0 | 30.7 ± 4.2 | 0.004 |
| TAPSE, mm | 17.7 ± 3.9 | 19.0 ± 4.2 | 0.084 |
| PASP, mmHg | 53.8 ± 11.6 | 41.7 ± 11.2 | <0.001 |
| Mitral regurgitation grade | | | |
| 1+, *n* (%) | 0 (0) | 0 (0) | 0.670 |
| 2+, *n* (%) | 1 (2.1) | 4 (4.0) | |
| 3+, *n* (%) | 20 (42.6) | 47 (47.5) | |
| 4+, *n* (%) | 26 (55.3) | 48 (48.5) | |
| Tricuspid regurgitation grade | | | |
| No, *n* (%) | 0 (0) | 55 (55.6) | <0.001 |
| Mild, *n* (%) | 0 (0) | 44 (44.4) | |
| Moderate, *n* (%) | 31 (66.0) | 0 (0) | |
| Severe, *n* (%) | 16 (34.0) | 0 (0) | |
| NYHA functional class | | | |
| I, *n* (%) | 0 (0) | 0 (0) | 0.019 |
| II, *n* (%) | 5 (10.6) | 23 (23.2) | |
| III, *n* (%) | 33 (70.2) | 70 (70.7) | |
| IV, *n* (%) | 9 (19.1) | 6 (6.1) | |

Categorical variables are expressed as *n* (%). Continuous variables are expressed as mean ± SD.
COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; EuroSCORE, European System for Cardiac Operative Risk Evaluation; STS, The Society of Thoracic Surgeons; MR, mitral regurgitation; LVEF, left ventricle ejection fraction; LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; TAPSE: tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure; NYHA: New York Heart Association.

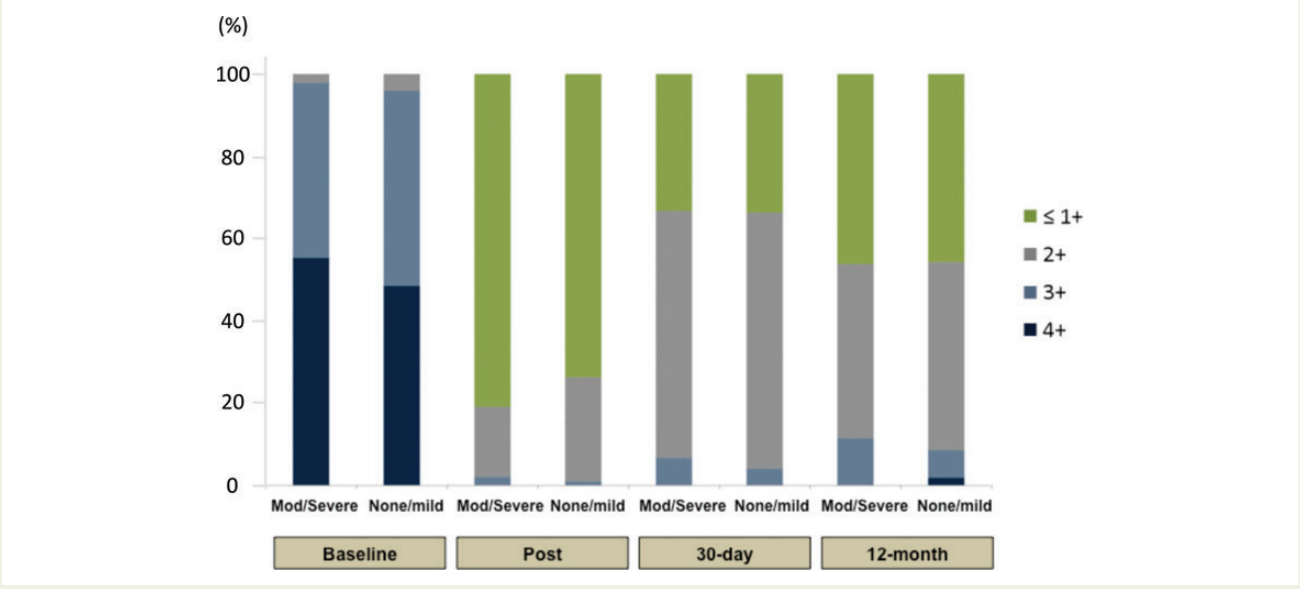


**Figure 1** Mitral regurgitation severity at baseline, post-procedure, 30-day, and 12-month.

the moderate/severe TR and none/mild TR groups (log-rank $P = 0.379$) (*Figure 4A*). The components of the primary efficacy endpoint when analysed separately were also similar between the two groups, but the estimates for freedom from combined death and re-hospitalization for HF were worse in the moderate/severe TR group compared with the none/mild TR group (67.7 vs. 88.8%, log-rank $P = 0.015$) (*Figure 4B–D*). While MR reduction was mostly sustained and equivalent through 12-month (*Table 3* and *Figure 1*) in the surviving patients from both groups, overall NYHA functional class was consistently worse in the moderate/severe TR group compared with the none/mild TR group (*Table 3* and *Figure 3*). The TR improvement observed early in the moderate/severe TR group was sustained in the surviving patients at the 12-month follow-up (*Table 3* and *Figure 2*).

Both groups demonstrated improved EF, as well as reduction of left ventricle systolic and diastolic volumes comparing baseline with the 12-month follow-up. PASP was significantly reduced in both groups in the same time frame (*Table 4*). Moreover, significant decrease in PASP was observed in patients who had improved TR grade (49.1 vs. 40.3 mmHg, baseline and 12-month, respectively, $P = 0.005$), whereas no significant change was observed in patients with no TR grade improvement (38.6 vs. 38.8 mmHg, baseline and 12-month, respectively, $P = 0.949$).

## Cox regression analysis

Predictive factors of mortality and re-hospitalization for HF were assessed using a Cox regression hazard model (*Table 5*). In the univariate analysis, baseline moderate/severe TR, chronic kidney disease, and atrial fibrillation were significant predictors of 12-month mortality and re-hospitalization. Likewise, the multivariable Cox regression model indicated baseline moderate/severe TR (adjusted HR: 2.67; 95% CI: 1.08–6.65; $P = 0.034$) and chronic kidney disease (adjusted HR: 3.16; 95% CI: 1.20–8.35; $P = 0.020$) as the only independent predictors of 12-month mortality and re-hospitalization.

## Association of TR and LVEF interaction on outcomes

To further assess the association between LVEF and TR, we divided our study population into two groups: patients with baseline LVEF $<35\%$ vs. LVEF $\geq 35\%$. Association of moderate/severe TR on mortality and re-hospitalization for HF was only observed in patients with baseline LVEF $<35\%$ (adjusted HR: 3.24; 95% CI: 1.07–9.80; $P = 0.038$).

# Discussion

PMVR with the MitraClip system has progressively established its role as an alternative treatment for high-risk surgical patients with moderate-to-severe and severe MR,[23] but the impact of baseline TR on the outcomes and its behaviour over time after MitraClip implantation are unknown. The rationale to better understanding this complex clinical setting is provided by the elevated rates of concomitant TR found in patients with FMR;[24] in addition, when moderate/severe TR is left untreated after surgery for FMR, it is associated with poor clinical outcomes compared with untreated none/mild TR;[15] therefore, both European and American guidelines give recommendation for tricuspid valve repair in patients undergoing mitral valve surgery with (i) severe TR (class I) and (ii) mild or moderate TR with dilated annulus (class IIa) or evidence of right HF (class II, American guideline only).[3,25] Conversely, the current standard practice of PMVR with MitraClip is based on isolated intervention in the mitral valve regardless of the baseline TR grade, hence, additional interest should be considered in the comprehensive elucidation of the association of moderate/severe TR on the outcomes after MitraClip implantation.

**Table 2 Thirty-day outcomes**

| Variable | Moderate/severe TR ($n = 47$) | None/mild TR ($n = 99$) | *P*-value |
|---|---|---|---|
| Primary safety endpoint | 5 (10.6) | 2 (2.0) | 0.035 |
| Death, *n* (%) | 2 (4.3) | 1 (1.0) | 0.243 |
| Myocardial infarction, *n* (%) | 0 (0) | 0 (0) | – |
| Surgery for failed MitraClip, *n* (%) | 0 (0) | 0 (0) | – |
| Emergent cardiovascular surgery, *n* (%) | 0 (0) | 0 (0) | – |
| Deep wound infection, *n* (%) | 0 (0) | 0 (0) | – |
| Mechanical ventilation for >48 h, *n* (%) | 0 (0) | 0 (0) | – |
| Gastrointestinal complication requiring surgery, *n* (%) | 0 (0) | 0 (0) | – |
| Stroke, *n* (%) | 1 (2.1) | 0 (0) | 0.322 |
| Renal failure after MitraClip, *n* (%) | 0 (0) | 0 (0) | – |
| New onset of atrial fibrillation, *n* (%) | 1 (2.1) | 0 (0) | 0.322 |
| Septicaemia, *n* (%) | 1 (2.1) | 0 (0) | 0.322 |
| Blood transfusion, *n* (%) | 1 (2.1) | 1 (1.0) | 0.542 |
| Primary efficacy endpoint | 45 (95.7) | 95 (96.0) | 0.630 |
| Re-hospitalization for heart failure, *n* (%) | 2 (4.3) | 0 (0) | 0.102 |
| Mitral regurgitation grade ($n = 143$)[a] | | | |
| 1+, *n* (%) | 15 (33.3) | 33 (33.7) | 0.800 |
| 2+, *n* (%) | 27 (60.0) | 61 (62.2) | |
| 3+, *n* (%) | 3 (6.7) | 4 (4.1) | |
| 4+, *n* (%) | 0 (0) | 0 (0) | |
| Tricuspid regurgitation grade ($n = 143$)[a] | | | |
| No, *n* (%) | 11 (24.4) | 51 (52.0) | <0.001 |
| Mild, *n* (%) | 22 (49.0) | 43 (43.9) | |
| Moderate, *n* (%) | 11 (24.4) | 4 (4.1) | |
| Severe, *n* (%) | 1 (2.2) | 0 (0) | |
| NYHA functional class ($n = 143$)[a] | | | |
| I, *n* (%) | 6 (13.3) | 28 (28.6) | 0.001 |
| II, *n* (%) | 24 (53.4) | 61 (62.2) | |
| III, *n* (%) | 14 (31.1) | 9 (9.2) | |
| IV, *n* (%) | 1 (2.2) | 0 (0) | |

Abbreviations as in *Table 1*.
[a]Results expressed based on $n = 143$ patients (i.e. dead patients were not included).
Categorical variables are expressed as *n* (%).

We demonstrated marked improvement in MR post-PMVR with MitraClip, which was mostly sustained through 12-month in the surviving patients of both groups, regardless of baseline TR severity; in addition, low rates of adverse events were revealed, confirming the feasibility and the mid-term efficacy and safety of this relatively novel intervention in this setting.[8,26] Early (i.e. 30-day) improvements in NYHA functional class were identified in both groups and remained stable over time, but the between-group differences that had been identified pre-procedure (i.e. worse functional class in the moderate/severe TR compared with none/mild TR group) were maintained through 12-month. Although this finding corroborates that MitraClip implantation leads to improvement in congestive HF symptoms even in patients with poor baseline functional class,[27] it suggests that when this feature is combined with moderate/severe TR, a limitation of the mid-term benefits usually obtained with the intervention might occur. We should acknowledge, however, that our follow-up time was limited, as one can speculate that patients with worse NYHA functional class would need an extended follow-up period to obtain optimal benefit of MitraClip implantation, hence, further assessments will be important to completely clarify these findings.

The reduction in TR magnitude observed after MitraClip implantation occurred early and was sustained over time. At 30-day and 12-month follow-up, respectively, 73.4 and 69.3% of the surviving patients initially included in the moderate/severe TR group had their TR grades reduced to none or mild, whereas the patients of the none/mild TR group revealed stable TR grades during the follow-up; nonetheless, the between-group differences identified at baseline were consistently observed through 12-month. Gaemperli *et al.*[28] had previously demonstrated that MitraClip implantation improves haemodynamic profiles by reducing LV preload while preserving contractility, ultimately leading to reduction in pulmonary capillary wedge pressure and increase in the cardiac index. Although direct haemodynamic assessments were not performed in our study, we assume that the TR performance after PMVR herewith described was largely a consequence of such haemodynamic improvements.[29] Indeed, significant decrease in PASP was observed in patients who had improved TR grade, whereas no significant change was observed in patients with no TR grade improvement, however, further investigation is warranted to better explain these mechanisms.[30] Owing to the limited follow-up time of this pivotal study, we were not able to evaluate whether the TR improvement/stability described in the early phase following MitraClip implantation remains unchanged in the long-term. This is particularly important, as Di Mauro *et al.*[15] previously demonstrated acute TR improvement but late (i.e. after a median interval time of 28 months) worsening in patients with untreated severe TR who underwent surgery for severe FMR; the authors revealed, moreover, that TR worsening at follow-up was associated with worse congestive HF symptoms and poor survival. In fact, we demonstrated utilizing Kaplan–Meir estimates that the moderate/severe TR group had a significantly worse performance in terms of freedom from death and re-hospitalization through 12-month (*Figure 4D*); furthermore, baseline moderate/severe TR was identified as an independent predictor of this combined outcome through 12-month. Although there was no statistically significant difference in mortality through the 12-month follow-up in our study groups [moderate/severe TR group (16.1%) compared with none/mild TR (8.8%) group ($P = 0.213$)], a type II statistical error cannot be ruled out, therefore, further investigations in larger populations are warranted. Neuhold *et al.* have previously shown the impact of TR on the outcome of medically managed congestive HF patients with mildly or moderately depressed LV function, however, when our study population was divided according to the baseline LVEF, association of moderate/severe TR on outcome was only observed in patients with baseline LVEF <35%.[19] As for FMR, secondary TR begets TR; therefore, patients with baseline LVEF <35% may be prone to develop biventricular failure. It is difficult

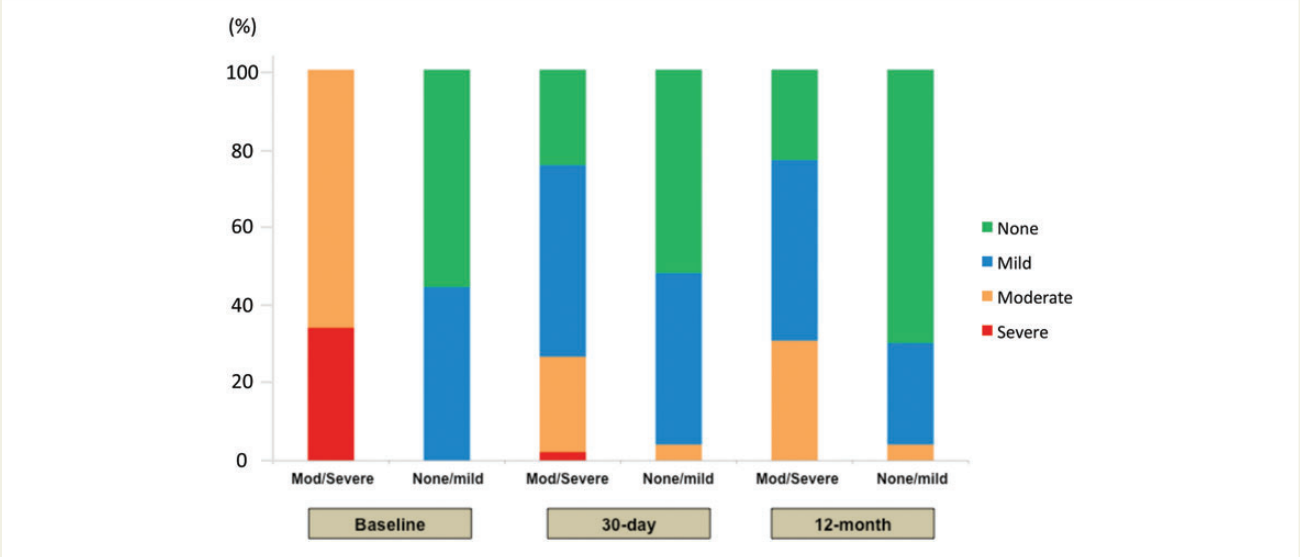


**Figure 2** Tricuspid regurgitation severity at baseline, 30-day, and 12-month.

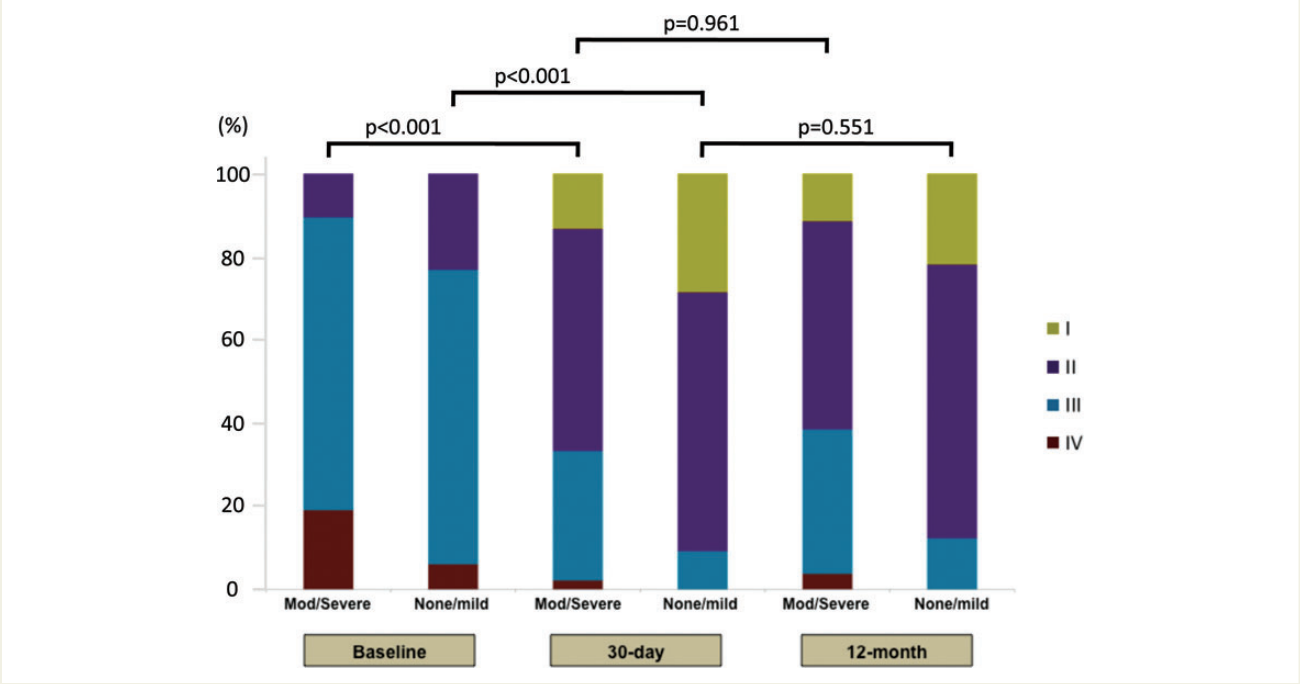


**Figure 3** NYHA functional class at baseline, 30-day, and 12-month. NYHA, New York Heart Association.

to prove, however, the impact of MitraClip implantation in this scenario, as we did not perform a direct comparison with clinically managed patients. Further investigation is warranted to completely elucidate these findings.

Left ventricle reverse remodelling has been consistently demonstrated after MitraClip implantation;[9,31] our findings are, therefore, in line with previous studies. In addition, we observed improvement in EF coupled with reduction in LV volumes regardless of baseline TR severity. Meanwhile, the reduction in the mitral valve area due to MitraClip implantation did not lead to important increase in mitral valve gradients, even if ~40% of the patients had more than one clip implanted. Importantly, PASP was significantly reduced in both groups through 12-month, which likely contributed to the TR improvement observed in our patients.[14] The implications of these findings with regard to treatment remain to be determined.

The current practice of MitraClip intervention does not include concomitant intervention in the tricuspid valve (i.e. in case of tricuspid annulus dilation or severe TR occurring in parallel to MR), as

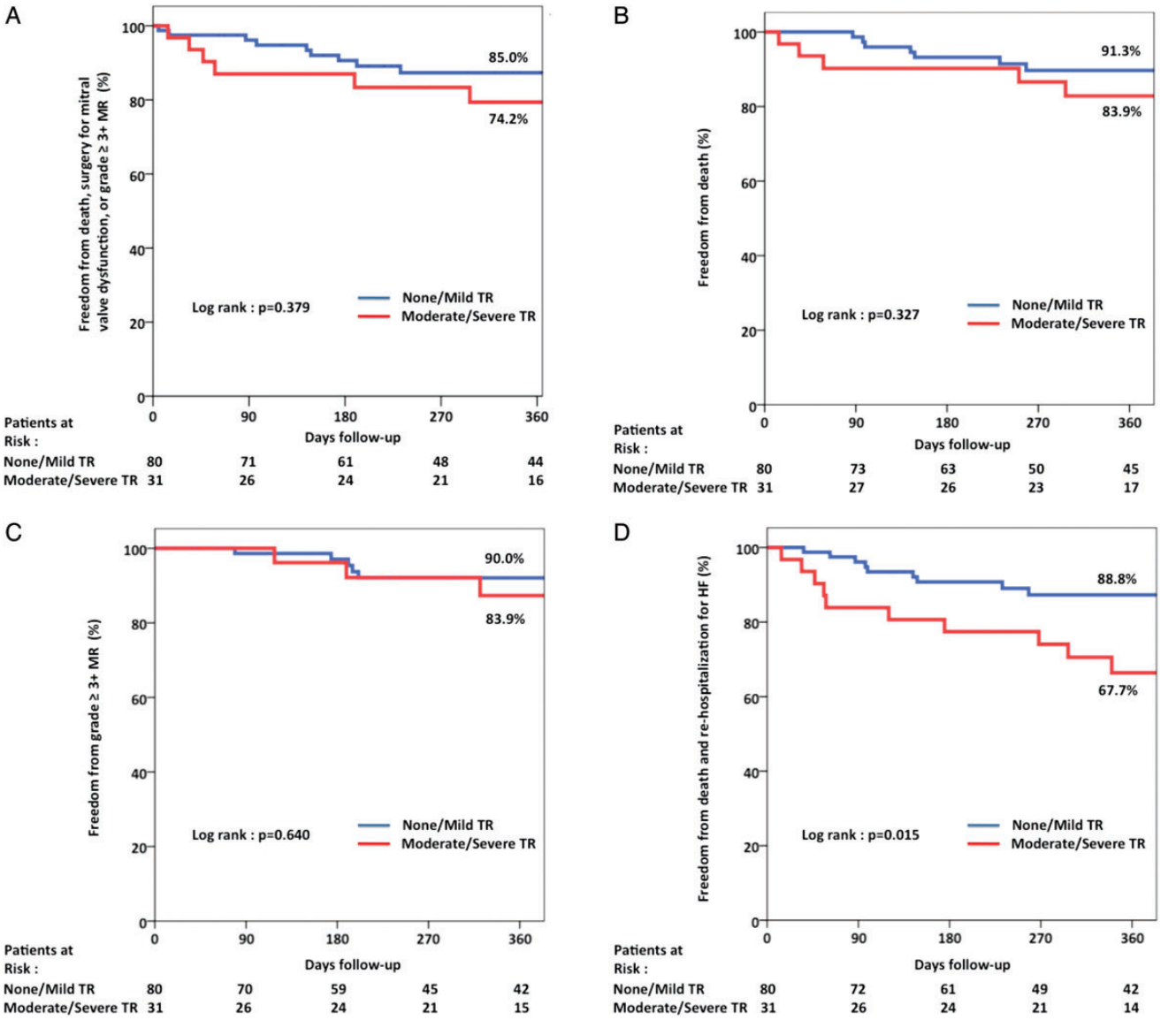


**Figure 4** Kaplan–Meier curves at 12-month follow-up. (*A*) Freedom from death, surgery for mitral valve dysfunction, or grade ≥ 3+ MR. (*B*) Freedom from death. (*C*) Freedom from MR ≥ 3+. (*D*) Freedom from death and re-hospitalization for HF. TR, tricuspid regurgitation; MR, mitral regurgitation; HF, heart failure.

percutaneous techniques are currently not well established in this clinical scenario.[32–34] Provided that a safe and efficacious percutaneous intervention is developed for the treatment of severe TR, we speculate that, when adequately indicated, the combination of these procedures could potentially refine the established benefits obtained with isolated MitraClip implantation. Further studies are warranted in this field.

**Table 3 Twelve-month outcomes**

| Variable | Moderate/severe TR ($n = 31$) | None/mild TR ($n = 80$) | *P*-value |
|---|---|---|---|
| MR ≥ 3+, *n* (%)[a] | 5 (16.1) | 8 (10.0) | 0.276 |
| Death, *n* (%)[a] | 5 (16.1) | 7 (8.8) | 0.213 |
| Surgery for mitral valve dysfunction[a] | 0 (0) | 0 (0) | – |
| Re-hospitalization for heart failure, *n* (%)[a] | 6 (19.4) | 2 (2.5) | 0.006 |
| Mitral regurgitation grade ($n = 99$)[b] | | | |
| 1+, *n* (%) | 12 (46.2) | 34 (46.6) | 0.935 |
| 2+, *n* (%) | 11 (42.3) | 34 (46.6) | |
| 3+, *n* (%) | 3 (11.5) | 5 (6.8) | |
| 4+, *n* (%) | 0 (0) | 0 (0) | |
| Tricuspid regurgitation grade ($n = 99$)[b] | | | |
| No, *n* (%) | 6 (23.1) | 51 (69.9) | <0.001 |
| Mild, *n* (%) | 12 (46.2) | 19 (26.0) | |
| Moderate, *n* (%) | 8 (30.7) | 3 (4.1) | |
| Severe, *n* (%) | 0 (0) | 0 (0) | |
| NYHA functional class ($n = 99$)[b] | | | |
| I, *n* (%) | 3 (11.5) | 16 (21.9) | 0.019 |
| II, *n* (%) | 13 (50.0) | 48 (65.8) | |
| III, *n* (%) | 9 (34.6) | 9 (12.3) | |
| IV, *n* (%) | 1 (3.8) | 0 (0) | |

Abbreviations as in *Table 1*.
[a]Results expressed based on $n = 111$ patients utilized for the calculation of the primary efficacy endpoint (i.e. including dead patients through the 12-month follow-up).
[b]Results expressed based on $n = 99$ patients (i.e. dead patients were not included).
Categorical variables are expressed as *n* (%).

## Study limitations

Our study has the inherent limitations of its retrospective design, although the data were collected prospectively. As a non-randomized study, several confounding factors could have influenced our results, but we performed statistical adjustment for the differences in baseline characteristics in order to minimize this potential caveat; indeed, the results were unchanged after doing so. We included a relatively small sample size with a limited (mid-term) follow-up which might have preclude strong multivariable analysis, but this was the first time the association of baseline TR as well as its behaviour over time were described after PMVR with MitraClip; nonetheless, we acknowledge that further investigation in larger populations and expanded follow-up is warranted. Although not all of our patients were available for the 12-month follow-up due to insufficient time elapsed since the index procedure, we utilized Kaplan–Meier estimates to assess our 12-month primary endpoint and its components. The interventions performed in this study were undertaken in a high-volume MitraClip implantation centre, hence, the results obtained should not be generalized. Tricuspid annulus diameter was not routinely obtained in our patients, therefore, the impact of this feature on patients that undergo MitraClip implantation remains to be determined. Furthermore, the haemodynamic consequences of post-procedural atrial septal defect due to the insertion of MitraClip 24 Fr-guiding catheter were not routinely obtained, but this information has been published recently.[35,36] The echocardiographic data herewith described were not reviewed by an independent core laboratory, as it was performed in a clinical setting, reflecting the real-world practice; however, the analyses were conducted by dedicated, highly experienced physicians[31] utilizing validated methods and were based on consensus, which we demonstrated low intra- and inter-observer variability for TR grading. The impact of the MitraClip procedure on eventual right ventricular function would be of interest,

**Table 4 Echocardiographic results at baseline and 12-month follow-up**

| Variable | Moderate/severe TR ($n = 26$) | | | None/mild TR ($n = 73$) | | |
|---|---|---|---|---|---|---|
| | Baseline | 12-month | *P*-value | Baseline | 12-month | *P*-value |
| LVEF, % | 32.1 ± 10.3 | 37.4 ± 9.3 | 0.004 | 34.4 ± 11.0 | 40.0 ± 7.6 | 0.021 |
| LVEDV, mL | 167.1 ± 51.0 | 137.1 ± 41.9 | 0.025 | 172.3 ± 75.0 | 144.8 ± 46.3 | 0.009 |
| LVESV, mL | 115.1 ± 48.6 | 88.2 ± 32.1 | 0.022 | 115.6 ± 65.5 | 90.9 ± 37.0 | 0.006 |
| Left atrial volume, mL | 100.3 ± 23.5 | 95.1 ± 23.5 | 0.428 | 97.2 ± 50.6 | 86.2 ± 21.6 | 0.090 |
| Mitral valve area, $cm^2$ | 4.27 ± 0.73 | 2.83 ± 0.80 | <0.001 | 4.08 ± 0.72 | 2.86 ± 0.60 | <0.001 |
| Mitral valve gradient, mmHg | 1.94 ± 0.83 | 3.70 ± 1.82 | <0.001 | 1.88 ± 0.85 | 3.74 ± 1.19 | <0.001 |
| Right atrial area, mm | 20.6 ± 4.6 | 21.6 ± 12.8 | 0.657 | 18.5 ± 4.6 | 18.1 ± 3.2 | 0.381 |
| Right ventricle diameter, mm | 33.7 ± 5.1 | 33.8 ± 3.7* | 0.974 | 30.5 ± 4.5 | 30.2 ± 4.0* | 0.872 |
| TAPSE, mm | 17.4 ± 3.5 | 18.9 ± 4.7 | 0.189 | 19.0 ± 4.3 | 19.3 ± 2.6 | 0.968 |
| PASP, mmHg | 54.3 ± 12.8 | 42.1 ± 8.1* | <0.001 | 41.6 ± 11.0 | 38.6 ± 6.9* | 0.046 |

Abbreviations as in *Table 1*. Inter-group comparison was also performed at 12-month follow-up and is indicated if the *P*-value was $< 0.05$*.

**Table 5 Baseline correlates for 12-month mortality and re-hospitalization rate**

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | *P*-value | Hazard ratio (95% CI) | *P*-value |
| Moderate/severe TR | 2.91 (1.18–7.16) | 0.020 | 2.67 (1.08–6.65) | 0.034 |
| Age (per 1-year increase) | 1.01 (0.98–1.04) | 0.669 | | |
| Male | 0.97 (0.37–2.56) | 0.955 | | |
| Atrial fibrillation | 2.78 (1.09–7.06) | 0.032 | 2.43 (0.95–6.23) | 0.064 |
| Chronic kidney disease | 3.07 (1.16–8.11) | 0.024 | 3.16 (1.20–8.35) | 0.020 |
| EuroSCORE II (per 1% increase) | 1.06 (0.99–1.12) | 0.286 | | |
| STS score (per 1% increase) | 1.04 (0.99–1.08) | 0.110 | | |
| LVEF (per 1% increase) | 0.97 (0.93–1.02) | 0.241 | | |
| PASP (per 1 mmHg increase) | 1.01 (0.97–1.04) | 0.726 | | |
| NYHA class (III/IV) | 5.32 (0.71–39.92) | 0.104 | | |

however, we could not perform precise assessment of the right ventricle using such as magnetic resonance imaging.

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**IMAGE FOCUS**

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# Chronic active Epstein–Barr virus infection complicated with multiple artery aneurysms

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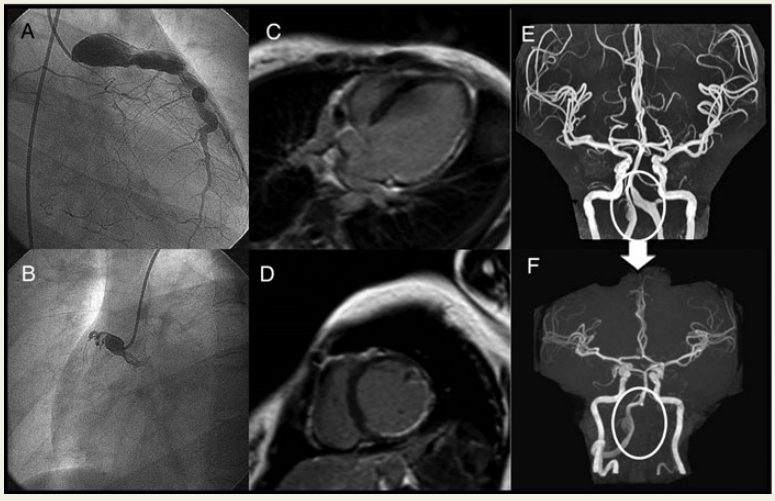


A 26-year-old woman was admitted to our hospital to undergo allogeneic peripheral blood stem cell transplantation for the treatment of chronic active Epstein–Barr virus (CAEBV) infection.

Transthoracic echocardiography showed hypokinetic inferior, posterior, and lateral left ventricular (LV) walls. Coronary angiography demonstrated large aneurysms in the proximal left (LCA) and right coronary arteries (RCA). The LCA aneurysm was located in the bifurcation of the left anterior descending (LAD) and left circumflex arteries (LCx), and the LCx was occluded at the diverging point from the left main coronary artery. The RCA was occluded by the distal portion of the aneurysm. Distal vessels to the occlusion sites of the LCx and RCA presented collateral vessels from the LAD (*Panels A* and *B*). Late gadolinium enhancement on cardiac magnetic resonance (MR) imaging revealed subendocardial enhancement within the LV walls, which corresponded with the occluded LCx and RCA territories (*Panels C* and *D*). Further screening was performed with MR angiography, which showed bilateral vertebral artery aneurysms (*Panel E*). Five months later, asymptomatic occlusion was also found in the left vertebral artery (*Panel F*).

Rarely, the primary infection of Epstein–Barr virus in T or natural killer cells induces CAEBV infection, a fatal syndrome characterized by infectious mononucleosis-like chronic symptoms that affect both children and young adults. Patients with CAEBV often develop multiple artery aneurysms, which are clinically silent until they rupture or cause organ damage. Therefore, screening for cardiovascular complications is indispensable in patients with CAEBV.