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ORIGINAL PAPER

Mitral regurgitation evolution after transcatheter tricuspid valve interventions—a sub-analysis of the TriValve registry

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Aims

Transcatheter tricuspid valve interventions (TTVI) are increasingly used to treat patients with significant tricuspid regurgitation (TR). The evolution of concurrent mitral regurgitation (MR) severity after TTVI is currently unknown and may be pivotal for clinical decision-making. The aim of this study was to assess the evolution of MR after TTVI and to identify predictors of MR worsening and improvement.

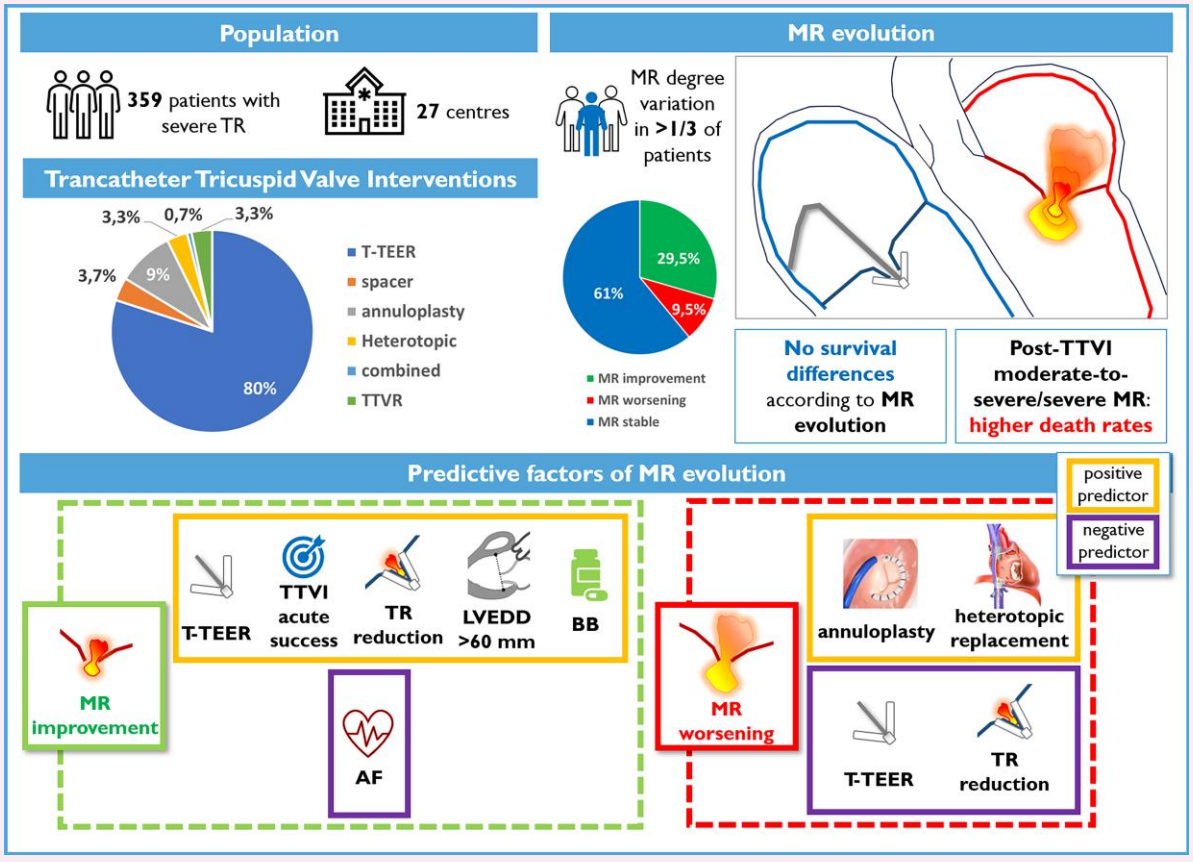
Methods and results

This analysis is a substudy of the TriValve Registry, an international registry designed to collect data on TTVI. This substudy included all patients with echocardiographic data on MR evolution and excluded those with a concomitant tricuspid and mitral transcatheter valve intervention or with a history of mitral valve intervention. The co-primary outcomes were MR improvement and worsening at two timepoints: pre-discharge and 2-month follow-up. This analysis included 359 patients with severe TR, mostly (80%) treated with tricuspid transcatheter edge-to-edge repair (T-TEER). MR improvement was found in 106 (29.5%) and 99 (34%) patients, while MR worsening was observed in 34 (9.5%) and 33 (11%) patients at pre-discharge and 2-month follow-up, respectively. Annuloplasty and heterotopic replacement were associated with MR worsening. Independent predictors of MR improvement were: atrial fibrillation, T-TEER, acute procedural success, TR reduction, left ventricular end-diastolic diameter> 60 mm, and beta-blocker therapy. Patients with moderate-to-severe/severe MR following TTVI showed significantly higher death rates.

Conclusion

MR degree variation is common after TTVI, with most cases showing improvement. Clinical and procedural characteristics may predict the MR evolution, in particular procedural success and T-TEER play key roles in MR outcomes. TTVI may be beneficial, even in the presence of functional MR.

Graphical Abstract



Mitral regurgitation evolution after TTVI. Abbreviations: AF, atrial fibrillation; BB, beta-blockers; LVEDD, left ventricular end-diastolic diameter; MR, mitral regurgitation; TR, tricuspid regurgitation; TTVI, transcatheter tricuspid valve interventions; TTVR, transcatheter tricuspid valve replacement; T-TEER, tricuspid-transcatheter edge-to-edge repair.

Keywords transcatheter tricuspid valve interventions • tricuspid regurgitation • mitral regurgitation • TriValve registry • tricuspid transcatheter edge-to-edge repair • ventricular interdependence

Introduction

Significant tricuspid regurgitation (TR) has a prevalence of around 4% in subjects over 75 years of age and is associated with impaired survival and heart failure symptoms.[1,2] In recent years, the development and successful results of various types of transcatheter therapies for TR have changed the management paradigm of a disease previously considered benign and often left untreated.[3–5]

Mitral regurgitation (MR), the second most common valvular heart disease after aortic stenosis, frequently coexists with significant TR in patients undergoing transcatheter tricuspid valve interventions (TTVI). However, the post-intervention evolution of MR, especially when TTVI is successful in reducing the degree of TR, is unknown. Conversely, a wealth of evidence is available regarding the evolution of TR after mitral valve repair (either surgical or percutaneous) or replacement, and current guidelines recommend concomitant surgical treatment of at least moderate TR during left-sided heart surgeries.[6–8] Similarly, concurrent TTVI in patients scheduled for mitral percutaneous repair for severe MR and significant TR has been associated with improved outcomes compared to isolated mitral intervention; however, no data are currently available on the opposite situation.[9]

Increasing severity of TR is associated with declining cardiac output,[2] while a significant increase in left ventricular (LV) preload and cardiac index has been observed in patients undergoing successful tricuspid valve (TV) surgery with functional improvement.[10] Physiological studies, instead, have demonstrated MR worsening in response to preload augmentation, especially in the setting of LV systolic disfunction[2,6]; however, it is unknown whether increased LV preload might translate into clinically relevant MR worsening after successful TTVI. Gaining insights regarding the trajectories of MR severity after TTVI may significantly contribute to clinical decision-making. Indeed, it would help to define whether patients undergoing TTVI may benefit from a concurrent transcatheter procedure on the mitral valve. Our objective was to investigate the evolution of MR after TTVI and to identify predictors of MR worsening and improvement.

Methods

Study design

This analysis is a sub-study of TriValve registry, an international observational study designed to collect data from centres across the world performing TTVI with different devices.[11,12] The TriValve registry was initiated in November 2016, and it is not supported by any external funding. A total of 27 international sites contributed to the retrospective and prospective collection of the registry data. All inconsistencies were resolved directly with local investigators and during on-site data monitoring. Baseline and intraprocedural clinical, anatomical, and echocardiographic data were collected. Pre-discharge and follow-up events and echocardiographic data were collected whenever available from the respective centres. The inclusion of patients in this study was approved in each centre by a local ethics committee or per local practice for the collection of retrospective data.

Definitions and outcomes

All the patients included in the TriValve registry had at least severe symptomatic TR according to the European or American guidelines for the management of heart valve disease and were treated according to local multidisciplinary team decision.[13,14] TR and MR severity grading was assessed according to European and American guidelines using a combination of semiquantitative and quantitative measurements.[7] Procedural success was defined as patient alive at the end of the procedure, with the device successfully implanted and delivery system retrieved, with a residual TR $\leq$ 2+.[11] Specific criteria and definitions for TTVI outcomes have been recently established by the Tricuspid Valve Academic Research Consortium (TVARC) in order to improve outcomes and unify practice, care, and definitions.[15]

The exclusion criteria included a concomitant tricuspid and mitral transcatheter valve intervention, a previous mitral valve surgical or transcatheter intervention, or the absence of echocardiographic data on MR degree at baseline and pre-discharge timepoint.

The co-primary outcomes were MR improvement and MR worsening after TTVI. MR improvement was defined as a reduction of at least 1 degree of MR severity. MR worsening was defined as an increase of at least 1 degree of MR severity.

The endpoint of survival analyses was all-cause death.

Statistical analysis

Continuous variables are reported as median (IQR) or mean (±SD) and compared using Student's *t*-test or the Mann–Whitney *U* or Wilcoxon test in case of two-group comparisons on the basis of normality of data distribution verified using the Kolmogorov–Smirnov goodness-of-fit test. In case of continuous variable comparisons between more than two groups, analysis of variance was performed. Bartlett's test for equal variances was performed to assess if the variances were comparable between groups. Categorical variables are reported as number (percentage) and compared using the χ^2 test without Yates' correction for continuity or the Fisher's exact test as appropriate. Paired analysis for ordinal data was performed using the Wilcoxon signed rank test with Bonferroni correction. OR and 95% CI for the co-primary outcomes were calculated with binary logistic regression. Univariate and multivariable logistic regression analyses were performed to test the multiplicative association between main baseline clinical, echocardiographic, and procedural variables and co-primary outcomes. Variables were excluded from the model in case of *P* values > 0.20. Survival analysis for MR evolution and MR degree was performed according to the Kaplan–Meier method using the log-rank test (Mantel Cox). Clinical follow-up was censored at the date of event or latest available follow-up. All variables included in the analyses were complete or had less than 15% of missing data. Two-sided *P* values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata (V.17.0).

Results

Population

The present analysis included a total of 359 patients with severe symptomatic TR, who underwent TTVI at 27 international sites between 2010 and 2023 and had an echocardiographic assessment at baseline and pre-discharge timepoints (*Figure 1*). Baseline characteristics of this primary population, stratified according to pre-discharge MR evolution, are shown in *Table 1*. Of these 359 patients, 288 had also an early post-discharge echocardiogram at 2-month timepoint. Baseline characteristics of this population, stratified according to 2-month MR evolution, are shown in *Table 2*. The TTVI included tricuspid transcatheter edge-to-edge repair (T-TEER) (Mitraclip, Triclip) in 80% ($n = 289$) of patients, annuloplasty (Cardioband, Tricinch, Trialign) in 9% ($n = 31$) of patients, spacer (Forma) in 3.7% ($n = 13$) of patients, combined T-TEER and annuloplasty procedure in 0.7% ($n = 2$), orthotopic transcatheter valve replacement (Navigate, V-dyne) in 3.3% ($n = 12$), and heterotopic transcatheter valve replacement (TricValve, Tricento, CAVI) in 3.3% ($n = 12$).

Mitral regurgitation

Baseline MR was none-to-mild in 59% ($n = 213$) of patients, moderate in 23% ($n = 81$), moderate-to-severe in 16% ($n = 57$), and severe in 2% ($n = 8$). The presence of a variation (at least 1 degree) of MR was analysed at two timepoints: pre-discharge (mean follow-up: 10 days) and 2-month (mean follow-up: 68 days) follow-up echocardiograms. Mitral regurgitation degree variations are shown in *Figure 2*. Mitral regurgitation worsening was observed in 9.5% ($n = 34$) of patients at pre-discharge and in 11% ($n = 33$) of patients at 2-month follow-up echocardiogram.

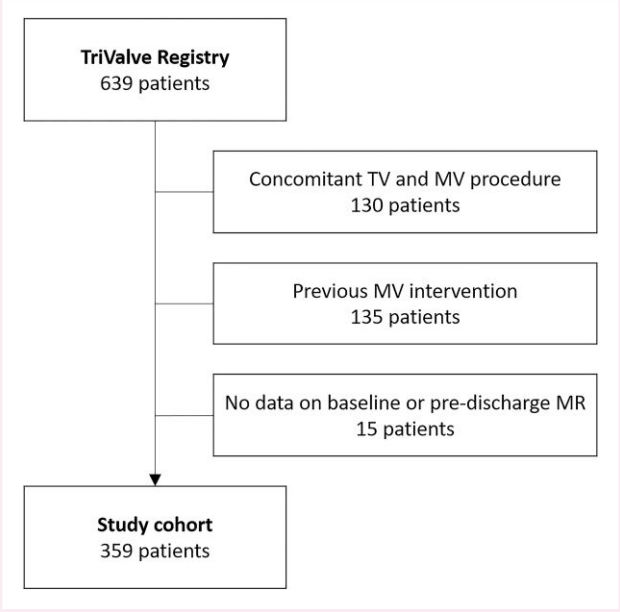


Figure 1 Flow-chart of study cohort selection. Abbreviations: MR, mitral regurgitation; MV, mitral valve; TV, tricuspid valve.

Mitral regurgitation worsening group at pre-discharge echocardiogram evolved at the 2-month timepoint as follows: 20 patients remained in the MR worsening group; 12 patients passed to MR stable group; and two patients passed to MR improvement group. Mitral regurgitation improvement occurred in 29.5% ($n = 106$) at pre-discharge and 34% ($n = 99$) of patients at 2-month follow-up echocardiogram. Mitral regurgitation improvement group at pre-discharge echocardiogram evolved at the 2-month timepoint as follows: 80 patients remained in the MR improvement group; nine patients passed to MR stable group; 3 patients passed to MR worsening group; and 14 patients did not have a 2-month echocardiographic assessment.

Mitral regurgitation worsening

Univariate analyses were performed to identify predictors of MR worsening at two timepoints (pre-discharge and 2-month follow-up) (*Table 3*; *Figure 3*). Mitral regurgitation worsening was observed in 9.5% of patients ($n = 34$) at pre-discharge and in 11% ($n = 33$) of patients at 2-month follow-up echocardiogram. The type of procedure had an impact on MR worsening, in particular a T-TEER procedure had a protective effect against MR worsening (at pre-discharge echo: OR 0.25, 95% CI 0.12–0.52). In contrast, transcatheter annuloplasty (at pre-discharge echo: OR 2.9, 95% CI 1.20–7.50) or heterotopic replacement is a predictor of MR worsening (at pre-discharge echo: OR 5.28, 95% CI 1.50–18.5; at 2-month follow-up: OR 8.65, 95% CI 2.05–36.4). Interestingly, an effective reduction of TR to at least moderate

Table 1 Baseline characteristics of the patient cohort stratified by mitral regurgitation evolution at pre-discharge echocardiogram

Demographics	Overall cohort ($n = 359$)	MR stable ($n = 219$)	MR improvement ($n = 106$)	MR worsening ($n = 34$)	*P* value
Age	78 (73–82)	77 (72–82)	80 (76–84)	80 (73–84)	**0.008**
Female	216 (60%)	138 (63%)	55 (52%)	23 (68%)	0.103
Body mass index	25 (22–28)	25 (22–28)	26 (23–28)	26 (22–30)	0.572
Previous myocardial infarction	56 (8%)	28 (14%)	22 (21%)	6 (18%)	0.210
COPD	75 (21%)	47 (22%)	22 (21%)	6 (18%)	0.964
Euroscore2	7 (4–14)	7 (4–14)	6 (4–15)	6 (5–10)	0.710
Atrial fibrillation	198 (55%)	138 (63%)	39 (37%)	21 (62%)	**<0.001**
PM/ICD	88 (25%)	49 (22%)	33 (31%)	6 (18%)	0.161
Chronic kidney disease	267 (74%)	160 (73%)	81 (76%)	26 (76%)	0.868
Diabetes mellitus	96 (27%)	52 (24%)	30 (28%)	14 (41%)	0.101
Right heart failure signs					
Ascites	74 (21%)	53 (25%)	14 (14%)	7 (23%)	0.061
Peripheral oedema	288 (80%)	166 (76%)	97 (91%)	25 (73%)	**0.003**
Therapy					
Baseline anti-RAAS therapy	214 (60%)	128 (58%)	67 (63%)	19 (56%)	0.657
Baseline beta-blocker therapy	291 (81%)	172 (79%)	91 (86%)	28 (82%)	0.305
Baseline MRA therapy	170 (47%)	99 (45%)	53 (50%)	18 (53%)	0.575
Baseline furosemide equivalent dose (mg)	88 (±112)	89 (±124)	84 (±89)	85 (±91)	0.668
2-month furosemide equivalent dose (mg)	72 (±78)	76 (±87)	61 (±47)	77 (±87)	0.623
Echocardiographic data					
TR aetiology					0.532
Functional atrial	162 (45%)	100 (46%)	48 (45%)	14 (41%)	
Functional ventricular	159 (44%)	94 (43%)	49 (46%)	16 (47%)	

Continued

Table 1 Continued

Demographics	Overall cohort (*n* = 359)	MR stable (*n* = 219)	MR improvement (*n* = 106)	MR worsening (*n* = 34)	*P* value
CIED	19 (5%)	14 (6%)	2 (2%)	3 (9%)	
Organic	19 (5%)	11 (5%)	7 (7%)	1 (3%)	
LVEF	55 (48–60)	55 (50–60)	51 (40–55)	55 (46–60)	**<0.001**
LVEF ≤ 30%	26 (7%)	7 (3%)	14 (13%)	5 (15%)	**0.001**
LVEDD	48 (43–53)	47 (49–53)	49 (44–54)	46 (43–51)	0.167
LVEDD > 60 mm	27 (7%)	12 (6%)	12 (15%)	3 (9%)	**0.045**
Left atrial volume	93 (69–126)	88 (65–116)	108 (78–144)	104 (70–125)	**0.017**
Baseline MR degree					**<0.001**
0	43 (12%)	33 (15%)	0	10 (29%)	
1	170 (47%)	140 (64%)	11 (10%)	19 (56%)	
2	81 (23%)	35 (16%)	42 (40%)	4 (12%)	
3	57 (16%)	11 (5%)	45 (42%)	1 (3%)	
4	8 (2%)	0	8 (8%)	0	
Pre-discharge MR degree					**<0.001**
0	48 (13%)	33 (15%)	15 (14%)	0	
1	224 (62%)	140 (64%)	76 (71%)	8 (20%)	
2	70 (20%)	35 (16%)	15 (14%)	20 (58%)	
3	14 (4%)	11 (5%)	0	3 (9%)	
4	3 (1%)	0	0	3 (9%)	
TAPSE	16 (14–19)	16 (13–20)	16 (13–18)	16 (15–19)	0.553
TAPSE/sPAP	0.40 (0.31–0.55)	0.40 (0.30–0.56)	0.41 (0.32–0.53)	0.39 (0.34–0.55)	0.767
TAPSE/sPAP < 0.4	144 (40%)	88 (47%)	41 (45%)	15 (56%)	0.595
Procedural data					
Procedure					**<0.001**
T-TEER	289 (80%)	174 (79%)	96 (91%)	19 (56%)	
Annuloplasty	31 (9%)	21 (9%)	3 (3%)	7 (21%)	
Spacer	13 (4%)	9 (4%)	3 (3%)	1 (3%)	
TTVR	12 (3%)	8 (4%)	1 (1%)	3 (9%)	
Heterotopic	12 (3%)	7 (3%)	1 (1%)	4 (12%)	
Combined	2 (1%)	0	2 (2%)	0	
Acute procedural success	298 (83%)	169 (77%)	103 (97%)	26 (76%)	**<0.001**
Low cardiac output syndrome	7 (2%)	5 (2%)	2 (2%)	0	0.659
Effective reduction to at least moderate TR	311 (87%)	183 (84%)	103 (97%)	25 (73%)	**<0.001**

Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; RAAS, renin–angiotensin–aldosteron; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annulus plane systolic excursion; T-TEER, tricuspid transcatheter edge-to-edge repair; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement.

degree resulted as a protective factor at pre-discharge follow-up (OR 0.48, 95% CI 0.23–0.99). The low number of events for the outcome MR worsening prevented the conduction of multivariable analyses.

Mitral regurgitation improvement

Univariate and multivariable analyses were performed to identify predictors of MR improvement at two timepoints (pre-discharge and 2-month follow-up) (*Table 4*; *Figure 4*). Mitral regurgitation improvement occurred in 29.5% of patients ($n = 106$) at pre-discharge and 34% of patients ($n = 99$) at 2-month follow-up echocardiogram. Dependent predictive factors of MR improvement were age, male gender, beta-blocker therapy, T-TEER procedure, acute procedural success, an effective reduction of TR to at least moderate degree, baseline and pre-discharge LVEDD, and baseline LVEF < 30%. Dependent preventive factors of MR improvement included baseline and pre-discharge LVEF and atrial fibrillation. A stepwise multivariable logistic analysis was used to test the multiplicative association between main baseline clinical, echocardiographic, and procedural variables and MR improvement at pre-discharge and 2-month follow-up echocardiogram (*Figure 4*). Procedural success and T-TEER resulted as independent predictors of MR improvement at pre-discharge echocardiogram. Instead, atrial fibrillation resulted as an independent preventive factor of MR improvement at pre-discharge follow-up. The independent predictors of

Table 2 Baseline characteristics of the patient cohort stratified by mitral regurgitation evolution at 2-month echocardiogram

Demographics	Overall cohort (*n* = 288)	MR stable (*n* = 156)	MR improvement (*n* = 99)	MR worsening (*n* = 33)	*P* value
Age	78 (74–82)	77 (72–82)	80 (75–83)	80 (75–82)	**0.007**
Female	172 (60%)	103 (66%)	51 (51%)	18 (55%)	0.057
Body mass index	25 (22–28)	25 (22–28)	25 (22–28)	25 (22–30)	0.957
Previous myocardial infarction	42 (15%)	20 (13%)	18 (18%)	4 (12%)	0.150
COPD	58 (20%)	29 (19%)	22 (22%)	7 (20%)	0.784
Euroscore2	6 (4–11)	5 (3–10)	6 (4–11)	6 (4–11)	0.228
Atrial fibrillation	152 (53%)	88 (56%)	45 (45%)	19 (57%)	0.356
PM/ICD	65 (18%)	35 (22%)	26 (26%)	6 (18%)	0.099
Chronic kidney disease	212 (74%)	118 (76%)	72 (72%)	22 (66%)	0.506
Diabetes mellitus	72 (25%)	36 (23%)	27 (27%)	9 (27%)	0.751
Right heart failure signs					
Ascites	49 (17%)	32 (22%)	8 (9%)	9 (29%)	**0.009**
Peripheral oedema	218 (76%)	111 (71%)	82 (82%)	25 (75%)	**0.044**
Therapy					
Baseline anti-RAAS therapy	180 (62%)	100 (64%)	64 (64%)	16 (48%)	0.209
Baseline beta-blocker therapy	244 (85%)	128 (82%)	91 (91%)	25 (75%)	**0.023**
Baseline MRA therapy	131 (45%)	69 (44%)	46 (46%)	16 (48%)	0.141
Baseline furosemide equivalent dose (mg)	81 (±99)	80 (±109)	74 (±73)	108 (±111)	0.129
2-month furosemide equivalent dose (mg)	67 (± 69)	71 (±74)	56 (±46)	78 (±94)	0.294
Echocardiographic data					
TR aetiology					0.320
Functional atrial	133 (46%)	72 (46%)	47 (47%)	14 (42%)	
Functional ventricular	122 (42%)	67 (43%)	43 (43%)	12 (36%)	
CIED	16 (6%)	10 (6%)	2 (2%)	4 (12%)	
Organic	17 (6%)	7 (5%)	7 (7%)	3 (10%)	
LVEF	55 (47–60)	55 (50–60)	52 (42–59)	55 (50–60)	**0.015**
LVEF ≤ 30%	19 (6%)	7 (5%)	10 (10%)	2 (6%)	0.212
LVEDD	48 (43–54)	48 (43–53)	50 (44–55)	48 (45–52)	0.401
LVEDD > 60 mm	26 (9%)	12 (6%)	12 (15%)	2 (6%)	0.191
Left atrial volume	99 (72–128)	94 (70–129)	104 (78–128)	95 (65–113)	0.314
Baseline MR degree					**<0.001**
0	39 (14%)	28 (18%)	0	11 (34%)	
1	126 (44%)	98 (63%)	10 (10%)	18 (56%)	
2	67 (23%)	27 (17%)	37 (37%)	3 (9%)	
3	48 (17%)	3 (2%)	44 (44%)	1 (3%)	
4	8 (3%)	0	8 (8%)	0	
2-month MR degree					**<0.001**
0	43 (14%)	28 (18%)	15 (15%)	0	
1	175 (61%)	98 (63%)	67 (68%)	10 (30%)	
2	62 (22%)	27 (17%)	17 (17%)	18 (55%)	
3	6 (2%)	3 (2%)	0	3 (9%)	
4	2 (1%)	0	0	2 (6%)	
TAPSE	16 (14–20)	16 (13–21)	16 (14–19)	17 (15–21)	0.313
TAPSE/sPAP	0.40 (0.31–0.6)	0.44 (0.30–0.62)	0.42 (0.31–0.56)	0.45 (0.34–0.60)	0.433
TAPSE/sPAP < 0.4	100 (35%)	53 (40%)	37 (42%)	10 (38%)	0.925
Procedural data					

Continued

Table 2 Continued

Demographics	Overall cohort (*n* = 288)	MR stable (*n* = 156)	MR improvement (*n* = 99)	MR worsening (*n* = 33)	*P* value
Procedure					0.055
T-TEER	242 (84%)	129 (83%)	87 (88%)	26 (78%)	
Annuloplasty	18 (6%)	10 (6%)	5 (5%)	3 (9%)	
Spacer	12 (4%)	9 (6%)	3 (3%)	0	
TTVR	6 (2%)	5 (3%)	1 (1%)	0	
Heterotopic	8 (3%)	2 (1%)	2 (2%)	4 (12%)	
Combined	2 (1%)	1 (1%)	1 (1%)	0	
Acute procedural success	246 (85%)	128 (82%)	92 (97%)	26 (78%)	**0.029**
Low cardiac output syndrome	5 (1%)	4 (2%)	1 (1%)	0	0.524
Effective reduction to at least moderate TR	215 (75%)	112 (72%)	82 (83%)	21 (63%)	**0.037**

Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; RAAS, renin–angiotensin–aldosteron; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annulus plane systolic excursion; T-TEER, tricuspid transcatheter edge-to-edge repair; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement.

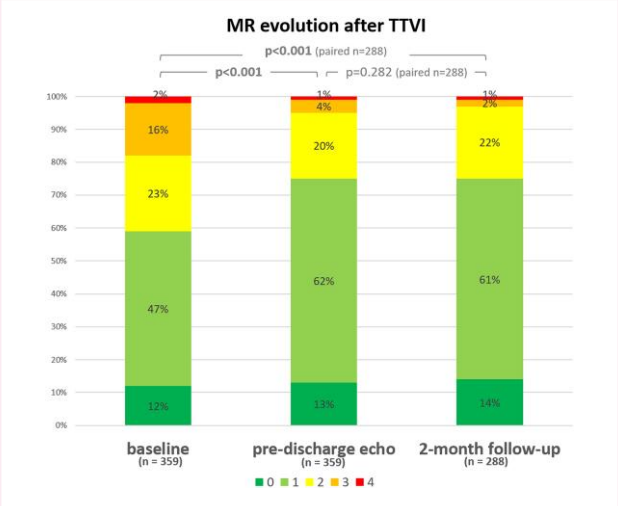


Figure 2 Mitral regurgitation evolution after transcatheter tricuspid valve intervention. Mitral regurgitation degree variations at three time-points (baseline, pre-discharge echocardiogram and 2-month follow-up) shown with bar plots. Abbreviations: MR, mitral regurgitation; TTVI, transcatheter tricuspid valve intervention.

MR improvement at 2-month follow-up were TR reduction, LVEDD > 60 mm, and beta-blocker therapy.

Prognostic impact of MR evolution and post-TTVI MR degree

Survival analysis for MR evolution and post-TTVI MR degree were performed according to the Kaplan–Meier method (*Figures 5–6*). Median follow-up was 246 days (113–390). The log-rank test did not detect any statistically significant difference among survival curves according to both stratifications (MR evolution and post-TTVI MR degree). Death rates at 12-month follow-up with stratification according to MR evolution and post-TTVI MR degree are shown in *Table 5* and *Figure 7*. Patients with moderate-to-severe/severe MR had a significantly higher death rate [5 (38.5%)] as compared with none-to-mild and moderate MR patients [respectively, 33 (13.2%) and 7 (10.8%)], while stratification based on MR evolution did not detect any statistically significant difference in terms of death rates.

Discussion

We aimed to investigate the evolution of MR after TTVI and to identify predictors of MR worsening and improvement. Our findings can be summarised as follows:

(1) more than one-third of patients undergoing TTVI shows a variation of MR degree after TTVI, and in most cases, it is an MR improvement;
(2) procedural success of TTVI results as a predictor of MR improvement;
(3) the type of transcatheter procedure has an impact on MR worsening and improvement;
(4) baseline characteristics associated with a ventricular functional MR subtype are associated with MR improvement;
(5) MR evolution has not a prognostic impact in this population, while a residual significant MR after TTVI is associated with higher death rates.

In recent years, the dawn of transcatheter interventions for TV has opened up new horizons for a wide cohort of 'forgotten patients' due to less invasive alternatives to surgical repair.[4,16] These interventions on the TV may trigger a cascade of hemodynamic changes involving also the left heart.[17,18] As a matter of fact, there exists an intricate hemodynamic interplay between TR and left heart, including the mitral valve.[17] Firstly, the onset of a significant TR causes right heart enlargement because of volume overload.[19] As a consequence of right heart congestion and dilatation, a certain degree of pericardial restraint develops and, due to the phenomenon of ventricular interdependence, left heart filling pressures increase.[10,20–22] Hence, increased right-sided pressures impair left ventricular filling, leading to reduced left ventricular compliance.[20,22] This, in turn, may result in an increase in the left atrial pressure and volume and in annular/valvular remodelling with worsening of functional MR. On this physiopathological basis, a successful TTVI procedure with a significant reduction of TR degree reduces

Table 3 Univariate analyses for MR worsening at both pre-discharge and 2-month echocardiographic assessment

Characteristics	OR (95% CI)	P	OR (95% CI)	P
	Pre-discharge ($n = 34$)		2-month follow-up ($n = 33$)	
Age	1.01 (0.97–1.06)	0.550	1.03 (0.97–1.08)	0.282
Male	0.69 (0.33–1.48)	0.351	1.27 (0.61–2.64)	0.520
CKD	1.12 (0.49–2.57)	0.790	0.67 (0.31–1.47)	0.319
PM/ICD	0.63 (0.25–1.58)	0.327	1.93 (0.90–4.16)	0.093
Diuretic therapy increase at 2-month			0.81 (0.29–2.24)	0.681
Diuretic therapy reduction at 2-month			1.50 (0.68–3.35)	0.317
Beta-blocker therapy	1.10 (0.44–2.77)	0.840	0.51 (0.22–1.23)	0.134
Anti-RAAS therapy	0.84 (0.41–1.72)	0.642	0.52 (0.25–1.08)	0.081
MRA therapy	1.28 (0.63–2.59)	0.494	1.99 (0.95–4.18)	0.068
T-TEER	**0.25 (0.12–0.52)**	**<0.001**	0.47 (0.20–1.08)	0.076
Annuloplasty	**2.90 (1.20–7.50)**	**0.020**	1.40 (0.39–5.06)	0.608
Orthotopic replacement	3.39 (0.87–13.20)	0.077		
Heterotopic replacement	**5.28 (1.50–18.5)**	**0.009**	**8.65 (2.05–36.4)**	**0.003**
Acute procedural success	0.63 (0.27–1.47)	0.289	0.59 (0.23–1.46)	0.256
TR reduction to at least moderate degree	**0.48 (0.23–0.99)**	**0.049**	0.60 (0.28–1.31)	0.202
Baseline LVEDD	0.98 (0.94–1.02)	0.369	0.99 (0.95–1.03)	0.833
Baseline LVEDD > 60 mm	1.12 (0.32–3.94)	0.864	0.58 (0.13–2.59)	0.476
Pre-discharge LVEDD	0.98 (0.94–1.03)	0.594	0.96 (0.92–1.01)	0.127
Delta LVEDD	1.01 (0.96–1.06)	0.687	0.96 (0.91–1.01)	0.135
Baseline LVEF	0.99 (0.96–1.02)	0.809	1.00 (0.97–1.04)	0.874
Baseline LVEF < 30%	2.47 (0.87–7.06)	0.089	0.89 (0.20–4.05)	0.882
Delta LVEF	0.97 (0.92–1.03)	0.337	0.99 (0.94–1.06)	0.882
Pre-discharge LVEF	0.98 (0.96–1.02)	0.385	0.99 (0.97–1.03)	0.986
Baseline TAPSE	0.98 (0.95–1.12)	0.411	1.00 (0.95–1.06)	0.400
Baseline TAPSE < 17 mm	1.41 (0.59–3.40)	0.433	1.17 (0.42–3.28)	0.754
TAPSE/sPAP	1.00 (0.98–1.02)	0.833	1.01 (0.99–1.02)	0.220
Baseline RV impairment (TAPSE/sPAP < 0.406)	1.45 (0.65–3.21)	0.356	0.90 (0.39–2.09)	0.824
Pre-discharge TAPSE	0.97 (0.88–1.08)	0.636	0.96 (0.85–1.07)	0.466
Atrial fibrillation	1.34 (0.65–2.77)	0.427	1.07 (0.51–2.22)	0.856

Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: CKD, chronic kidney disease; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; RAAS, renin–angiotensin–aldosteron; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annulus plane systolic excursion; T-TEER, tricuspid transcatheter edge-to-edge repair; TR, tricuspid regurgitation.

the right heart chambers' volumes[10] and pressures and may restore normal interventricular interactions, with an increase of right heart output and a reduction of left heart filling pressures, as recently shown by Kresoja et al. in the HERACLES-HFpEF trial.[22] The reduction of left atrial pressures may reduce the annular dilatation mechanism, while the normalization of interventricular septum position may restore the normal closing forces on the leaflets.

Hence MR—above all if functional—may improve as a consequence of TR treatment. In our analysis, an updated classification of MR mechanisms was not present; however, it is likely that almost all patients undergoing isolated TTVI had only functional MR. Moreover, some 'ventricular functional' key factors (LVEDD, LVEF) were significantly associated with MR improvement at the univariate analyses. Successful TR treatment is associated with stabilization of loop diuretic dose[18], and the improvement in cardiac output may allow optimization of guideline-directed medical therapy for heart failure, which in turn may lead to further MR improvement, in addition to the haemodynamic and physiopathological mechanisms described above.[23,24] Similarly, beta-blockers emerged as predictors of MR improvement. Indeed, after successful TTVI and reduction of ventricular interdependence, beta-blocker therapy may improve diastolic filling and, according to Frank–Starling law, enhance forward stroke volume with a beneficial effect on mitral regurgitation.

In contrast, the presence of atrial fibrillation was associated with lack of improvement of MR after TTVI. Functional atrial TR or MR is driven by annular dilatation with insufficient leaflet remodelling in the context of long-standing atrial fibrillation.[19] Conversely, progressive worsening of the degree of regurgitation and the resulting atrial dilatation make sinus rhythm restoration harder to achieve in a vicious circle. Active restoration of sinus rhythm has demonstrated to promote reverse atrial and ventricular remodelling and determine a reduction in severity of MR and/or TR;[20] however, the role of cardioversion or atrial fibrillation ablation in the context of TTVI has not yet been established.

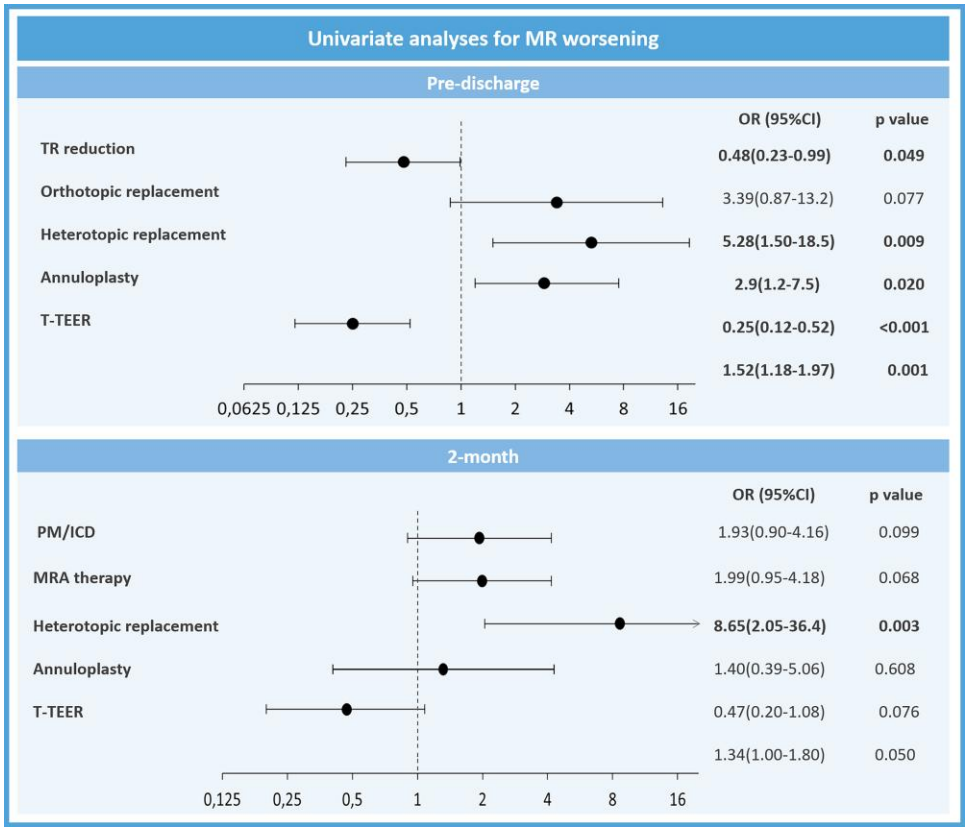


Figure 3 Forest plot for univariate analyses for mitral regurgitation worsening. Abbreviations: ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; TR, tricuspid regurgitation; T-TEER, tricuspid transcatheter edge-to-edge repair.

Table 4 Univariate analyses for the outcome MR improvement at both pre-discharge and 2-month echocardiographic assessment

Characteristics	OR (95% CI)	*P*	OR (95% CI)	*P*
	Pre-discharge ($n = 106$)		2-month follow-up ($n = 99$)	
Age	**1.04 (1.01–1.07)**	**0.002**	**1.06 (1.01–1.08)**	**0.008**
Male	**1.62 (1.02–2.56)**	**0.022**	**1.67 (1.02–2.74)**	**0.041**
CKD	0.82 (0.49–1.35)	0.438	0.91 (0.52–1.58)	0.750
PM/ICD	1.39 (0.85–2.29)	0.193	1.26 (0.72–2.21)	0.410
Diuretic therapy increase at 2-month			0.98 (0.52–1.86)	0.963
Diuretic therapy reduction at 2-month			1.16 (0.68–1.97)	0.580
Beta-blocker therapy	1.59 (0.88–2.90)	0.127	**2.68 (1.19–6.01)**	**0.017**
Anti-RAAS therapy	1.21 (0.77–1.90)	0.402	1.15 (0.69–1.91)	0.586
MRA therapy	1.17 (0.75–1.82)	0.482	1.06 (0.65–1.73)	0.809
T-TEER	**2.15 (1.14–4.05)**	**0.018**	1.88 (0.91–3.88)	0.087
Annuloplasty	0.75 (0.34–1.66)	0.474	0.80 (0.29–2.17)	0.670
Orthotopic replacement	0.18 (0.03–1.40)	0.101	0.37 (0.04–3.26)	0.374
Heterotopic replacement	0.67 (0.18–2.53)	0.557	0.63 (0.12–3.17)	0.574
Procedural success	**3.3 (1.58–7.02)**	**0.002**	**2.98 (1.27–6.99)**	**0.012**
TR reduction to at least moderate degree	**2.26 (1.29–3.92)**	**0.004**	**2.29 (1.22–4.33)**	**0.010**
Baseline LVEDD	**1.06 (1.03–1.09)**	**<0.001**	1.02 (0.99–4.77)	0.125

Continued

Table 4 Continued

Characteristics	OR (95% CI)	P	OR (95% CI)	P
	Pre-discharge ($n = 106$)		2-month follow-up ($n = 99$)	
LVEDD > 60 mm	**2.27 (1.02–5.07)**	**0.045**	2.09 (0.92–4.77)	0.077
Pre-discharge LVEDD	**1.05 (1.02–1.08)**	**0.002**	**1.04 (1.01–1.06)**	**0.027**
Delta LVEDD	0.98 (0.95–1.02)	0.399	1.02 (0.98–1.06)	0.302
Baseline LVEF	**0.96 (0.94–0.98)**	**<0.001**	**0.96 (0.94–0.98)**	**0.002**
Baseline LVEF < 30%	**3.01 (1.36–6.89)**	**0.007**	2.2 (0.88–5.73)	0.090
Delta LVEF	0.99 (0.95–1.02)	0.518	1.00 (0.97–1.05)	0.822
Pre-discharge LVEF	**0.96 (0.94–0.98)**	**<0.001**	**0.97 (0.95–0.99)**	**0.005**
Baseline TAPSE	0.96 (0.91–1.01)	0.129	0.95 (0.89–1.01)	0.078
Baseline TAPSE < 17 mm	1.54 (0.76–3.11)	0.228	2.20 (0.89–5.37)	0.086
Baseline RV impairment (TAPSE/sPAP < 0.406)	1.45 (0.66–3.21)	0.356	1.10 (0.65–1.87)	0.710
Pre-discharge TAPSE	1.04 (0.97–1.09)	0.244	1.03 (0.96–1.10)	0.336
Atrial fibrillation	**0.46 (0.29–0.73)**	**0.001**	0.78 (0.47–1.27)	0.319

Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; RAAS, renin–angiotensin–aldosteron; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annulus plane systolic excursion; T-TEER, tricuspid transcatheter edge-to-edge repair.

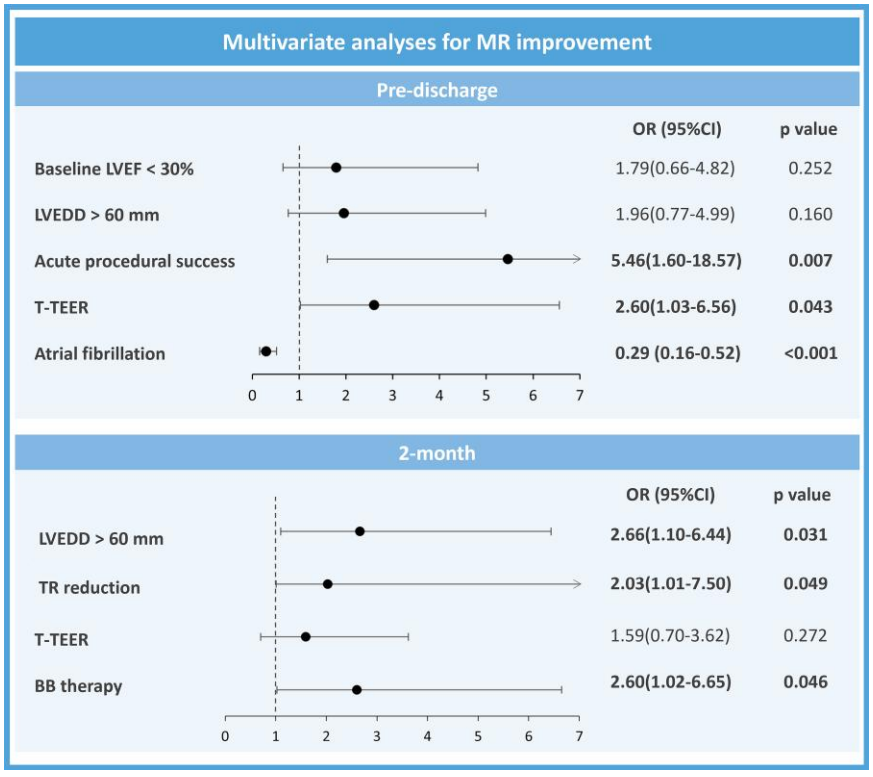


Figure 4 Forest plots for multivariable analyses for mitral regurgitation improvement.* Abbreviations: BB, beta-blocker; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; T-TEER, tricuspid transcatheter edge-to-edge repair; TR, tricuspid regurgitation. *: only variables with $P < 0.300$ are shown. The multivariable analyses included the following covariates: pre-discharge: baseline LVEF < 30%, baseline LVEDD > 60 mm, baseline TAPSE < 17 mm, acute procedural success, T-TEER, orthotopic replacement, beta-blocker therapy, atrial fibrillation; 2-month follow-up: baseline LVEDD > 60 mm, baseline LVEF < 30%, baseline TAPSE < 17 mm, TR reduction to at least moderate degree, acute procedural success, T-TEER, beta-blocker therapy.

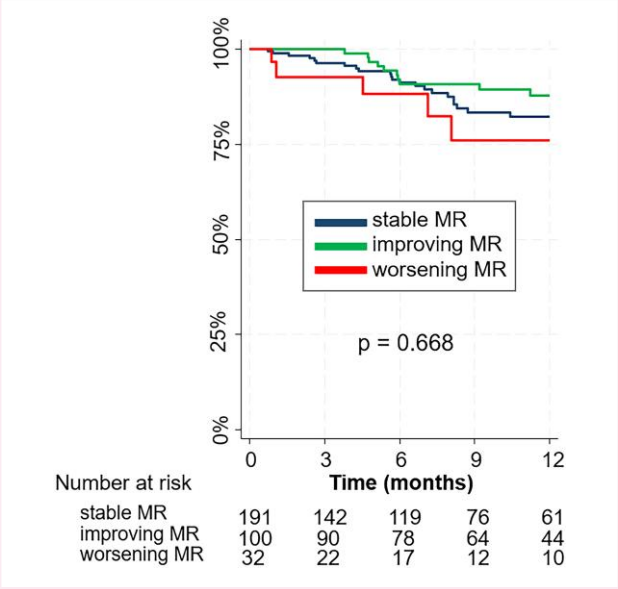


Figure 5 Kaplan–Meier survival curve according to pre-discharge MR evolution. Abbreviations: MR, mitral regurgitation.

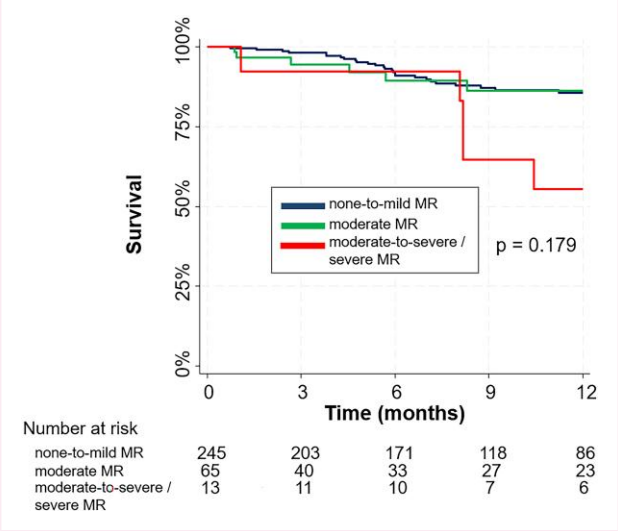


Figure 6 Kaplan–Meier survival curve according to post-TTVI MR degree. Abbreviations: MR, mitral regurgitation; TTVI, tricuspid transcatheter valve interventions.

Of note, the type of transcatheter procedure has shown to significantly influence MR outcomes. In particular, the T-TEER procedure, which was by far the most performed type of TTVI in our study, has shown a preventive role against MR worsening, while the transcatheter annuloplasty and the heterotopic valve replacement resulted as predictors of MR worsening.[25,26] This difference may be the expression of currently better outcomes and procedural results with the T-TEER approach as compared with transcatheter annuloplasty. In contrast, heterotopic valve replacement does not target the valvular disease, while it has a role for peripheral congestion and symptom control. Accordingly, successful T-TEER has demonstrated to be associated with significant reverse remodelling with improvements in the right chamber size and function at 1-year follow-up[21]; conversely, heterotopic valve replacement has not yet demonstrated significant improvements in haemodynamic parameters or RV volumes.[27]

At survival analysis, the MR evolution variable, either improvement or worsening, failed to show a significant prognostic impact. The prognosis of such a complex and diverse population is likely driven by many concurring factors, and the MR evolution may represent a marker of the hemodynamic interplay between left and right heart and of the effect of TTVI. It is noteworthy that in our analysis, baseline MR was severe only in 2% of cases; hence, our results do not apply to patients with concomitant severe MR and TR. In contrast, the death rates at 12-month follow-up are significantly higher in patients with residual moderate-to-severe or severe MR after TTVI, underscoring the well-established prognostic role of significant MR also in this population.

In conclusion, even if larger and more homogeneous studies are needed, our analysis is the first to inform clinicians and interventionalists regarding the evolution of MR in cases of severe TR treated with TTVI. Our results are overall reassuring as most cases of 'evolving MR' show an improvement, above all if TTVI is successful and if baseline characteristics associated with a ventricular functional MR subtype are present. Moreover, an effective TTVI with significant TR reduction may prevent MR worsening and possibly trigger an improvement of MR, differently from the common belief (i.e. MR worsening in response to preload augmentation).[2,6] Hence, the presence of a significant functional MR should not impede the use of TTVI for severe symptomatic TR.

Limitations

Our findings should be interpreted in light of some limitations. Firstly, the present study is a sub-analysis of the TriValve registry, which is a nonrandomized study without a control group. Hence, selection and confounding bias cannot be excluded because of the observational nature of our study. Secondly, this registry gathers real-world data, clearly mirroring the clinical practice in different centres worldwide; therefore, echocardiographic and clinical data have been reported without core lab adjudication, and the modalities of follow-up were different

Table 5 Death rates stratified by MR evolution and post-TTVI MR degree

	MR stable ($n = 197$)	MR improvement ($n = 100$)	MR worsening ($n = 32$)	*P* value
Death	27 (13.7%)	13 (13.0%)	5 (15.6%)	0.940
	None-to-mild MR ($n = 251$)	**Moderate MR ($n = 65$)**	**Moderate-to-severe/severe MR ($n = 13$)**	***P* value**
Death	33 (13.2%)	7 (10.8%)	5 (38.5%)	**0.044**

Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: MR, mitral regurgitation; TTVI, transcatheter tricuspid valve interventions.

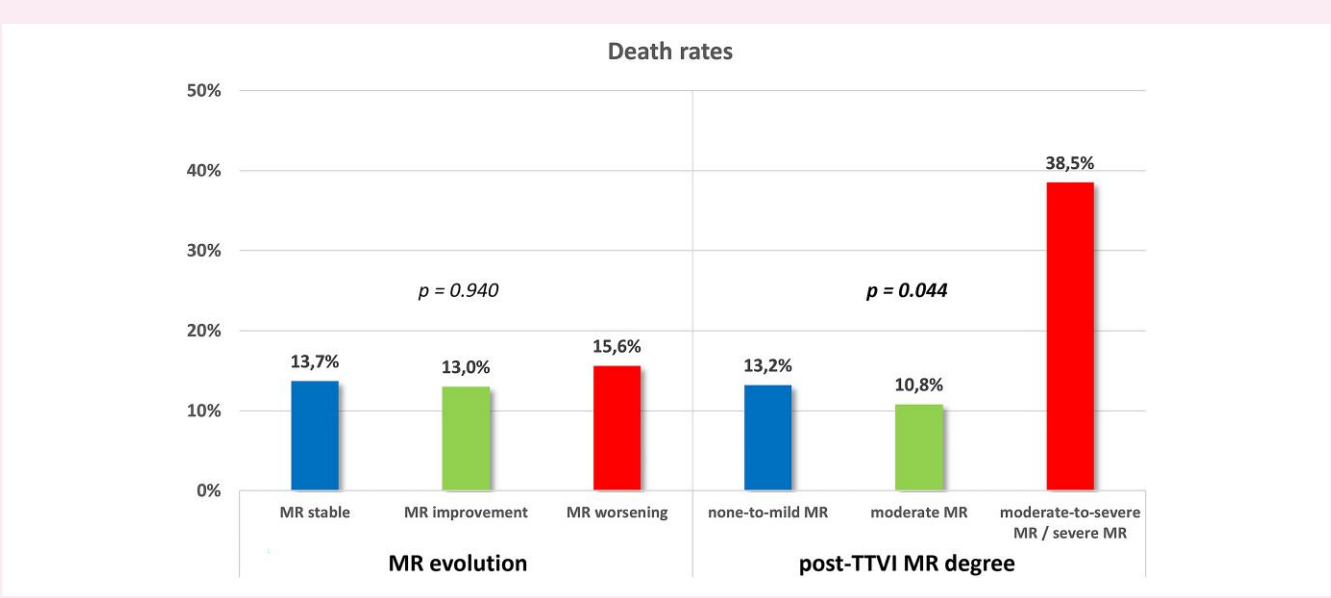


Figure 7 Death rates according to MR evolution and post-TTVI MR degree. Abbreviations: MR, mitral regurgitation; TTVI, transcatheter tricuspid valve interventions.

according to the local policy. Then, most patients were treated with a T-TEER procedure, in particular with MitraClip device in an early phase of T-TEER international experience and with a sharp predominance of TriClip device during the last years. This procedural imbalance may influence our analyses and inferences. Moreover, our analyses and results may be limited by a relatively small sample size. The incomplete echocardiographic follow-up at 2-month timepoint may hinder our inferences; however, the substantial similarity of MR evolution predictors at the two timepoints is a proof of the robustness of our results. Lastly, the observational nature of our findings cannot support a cause–effect relationship between TTVI and MR variation due to potential unmeasured confounders.

Conclusions

In this sub-analysis of TriValve registry, MR evolution after TTVI is present in more than one-third of the patients and in most cases is a reduction of MR severity. Procedural success of TTVI procedure with TR reduction and a transcatheter edge-to-edge repair approach have a favourable impact on MR evolution, together with baseline characteristics depicting a ventricular functional MR subtype. Even if updated data from larger and more uniform populations are warranted, this analysis may inform clinicians in the therapeutic pathway planning of patients with significant TR and concomitant MR.

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Conflict of interest: RH has served as a consultant for Abbott Vascular, Abbott Structural, NaviGate, Philips Healthcare, Medtronic, Edwards Lifesciences, and GE Healthcare; has been the Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-supported trials, for which she receives no direct industry compensation; has received speaker fees from Boston Scientific and Baylis Medical; and has received non-financial support from 3mensio. HA has received consulting fees from Abbott and Edwards LifeSciences. MA has served as a proctor/consultant for and has received speaker fees from Abbott, Edwards LifeSciences, Boston, Zoll, and Medtronic; and has received institutional grants from Edwards Lifesciences, Abbott, Medtronic, and LSI Solutions. DB has received speaker honoraria and travel support from Abbott Vascular. KC has received honoraria from Abbott. PD has served as a consultant for Abbott Vascular, 4Tech, Neovasc, and InnovHeart; and has received honoraria from Abbott and Edwards Lifesciences. RE-L has received speaker fees from Abbott, Boston, and Edwards Lifesciences. JH has received speaker honoraria from Abbott Vascular and Edwards Lifesciences. DH has served as proctor for Edwards Lifesciences and Abbott Vascular. DK has received personal fees from Abbott Medical, Edwards Lifescienes, Medtronic Inc., and Pi-Cardio Ltd. outside the submitted work. MA has been a consultant to Abbott Structural Heart and Medtronic. AL has served on the advisory board for Medtronic, Abbott Vascular Boston Scientific, Edwards Lifesciences, Shifamed, NeoChord Inc., V-dyne, and Philips. EL has received grant support and lecture fees from Abbott; and has received lecture fees from Edwards Lifesciences. SL has received travel compensation from Edwards LifeSciences, advisory fees from Bayer, speaker honoraria from Abbott and serves as consultant for New Valve Technology. PL has received speaker fees from Abbott. FP has received travel expenses from Edwards Lifesciences, Abbott Vascular, and Polares Medical. JR-C has received institutional research grants from Edwards Lifesciences. JS has served as a consultant for Edwards Lifesciences. HS has received study honoraria, travel expenses, and consulting fees from 4Tech Cardio, Abbott, Ablative Solutions, Ancora Heart, Bavaria Medizin Technologie, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, Celonova, Comed BV, Contego, CVRx, Edwards Lifesciences, Endologix, Hemoteq, Lifetech, Maquet Getinge Group, Medtronic, Mitralign, Nuomao Medtech, Occlutech, PFM Medical, ReCor, Renal Guard, Rox Medical, Terumo, Vascular Dynamics, and Vivasure Medical. GT has served as a consultant, physician advisory board member, and faculty trainer for Abbott Structural Heart; has served as a consultant for Medtronic and NeoChord; and has served as a physician advisory board member for JenaValve. K-PK has been a consultant to Edwards Lifesciences. MM has received the following personal fees of minimal amounts since January 2021: from Amgen, Liva Nova, and Vifor pharma as a member of Executive or Data Monitoring Committees

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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