

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

Francesco Cannata <sup>1\*</sup>†, Alessandro Sticchi<sup>2,3†</sup>, Giulio Russo <sup>4</sup>, Kamil Stankowski<sup>5,6</sup>, Rebecca T. Hahn<sup>7</sup>, Hannes Alessandrini<sup>8</sup>, Martin Andreas<sup>9</sup>, Daniel Braun <sup>10</sup>, Kim A. Connelly <sup>11</sup>, Paolo Denti <sup>12</sup>, Rodrigo Estevez-Loureiro<sup>13</sup>, Neil Fam<sup>11</sup>, Claudia Harr<sup>8</sup>, Joerg Hausleiter<sup>10</sup>, Dominique Himbert<sup>14</sup>, Daniel Kalbacher<sup>15,16</sup>, Marianna Adamo <sup>17</sup>, Azeem Latib<sup>18</sup>, Edith Lubos<sup>15</sup>, Sebastian Ludwig <sup>15,16</sup>, Philipp Lurz<sup>19</sup>, Vanessa Monivas<sup>20</sup>, Georg Nickenig<sup>21</sup>, Giovanni Pedrazzini<sup>22,23</sup>, Alberto Pozzoli<sup>24</sup>, Fabien Praz <sup>25</sup>, Josep Rodes-Cabau <sup>26</sup>, Karl-Philipp Rommel<sup>27</sup>, Joachim Schofer<sup>8</sup>, Horst Sievert<sup>28</sup>, Gilbert Tang<sup>29</sup>, Holger Thiele <sup>27</sup>, Karl-Patrik Kresoja<sup>19</sup>, Marco Metra <sup>17</sup>, Ralph Stephan von Bardeleben<sup>19</sup>, John Webb<sup>30</sup>, Stephan Windecker <sup>25</sup>, Martin Leon<sup>7</sup>, Francesco Maisano <sup>12</sup>, Federico De Marco<sup>31</sup>, Gianluca Pontone <sup>1,32</sup>, and Maurizio Taramasso <sup>33</sup>

<sup>1</sup>Department of Perioperative Cardiology and Cardiovascular Imaging, Centro Cardiologico Monzino IRCCS, Milan, Italy; <sup>2</sup>Cardiac Catheterisation Laboratory, Cardiothoracic and Vascular Department, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; <sup>3</sup>Dipartimento di Patologia Chirurgica, Medica, Molecolare e dell'Area Critica, University of Pisa, Pisa, Italy; <sup>4</sup>Policlinico Tor Vergata, Cardiology Unit, University of Rome, Italy; <sup>5</sup>Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, 4, 20090 Pieve Emanuele, Milano, Italy; <sup>6</sup>Cardio Center, IRCCS Humanitas Research Hospital, Via Alessandro Manzoni, 56, 20089 Rozzano, Milano, Italy; <sup>7</sup>Division of Cardiology, The New York-Presbyterian/Columbia University Irving Medical Center, New York, NY, USA; <sup>8</sup>MVZ Structural Heart Department, Asklepios Clinic St. Georg, Hamburg, Germany; <sup>9</sup>Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria; <sup>10</sup>Medical Clinic and Polyclinic I, University Hospital of Munich, Munich, Germany; <sup>11</sup>Division of Cardiology, St. Michael's Hospital, Toronto, Ontario, Canada; <sup>12</sup>Division of Cardiology and Department of Cardiac Surgery, San Raffaele University Hospital, Milan, Italy; <sup>13</sup>Interventional Cardiology Clinic, University Hospital Alvaro Cunqueiro, Vigo, Spain; <sup>14</sup>Division of Cardiology, Bichat Hospital, Paris, France; <sup>15</sup>Department of Cardiology, University Medical Center Hamburg-Eppendorf, University Heart & Vascular Center Hamburg, Martinistr. 52, 20246 Hamburg, Germany; <sup>16</sup>German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany; <sup>17</sup>Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; <sup>18</sup>Division of Cardiology, Montefiore Medical Center, New York, NY, USA; <sup>19</sup>Division of Cardiology, University Medical Center, Mainz, Germany; <sup>20</sup>Division of Cardiology, Puerta de Hierro University Hospital, Madrid, Spain; <sup>21</sup>Heart Center, University Hospital Bonn, Bonn, Germany; <sup>22</sup>Division of Cardiology, Cardiocentro Ticino Institute, EOC, Lugano, Switzerland; <sup>23</sup>Biomedical Faculty, Università della Svizzera Italiana (USI), Lugano, Switzerland; <sup>24</sup>Unit of Cardiac Surgery, Cardiocentro Ticino Institute, EOC, Lugano, Switzerland; <sup>25</sup>Department of Cardiology, Cardiovascular Center, Inselspital, Bern University Hospital, Bern, Switzerland; <sup>26</sup>Department of Cardiology, Quebec Heart and Lung Institute, Laval University, Quebec City, Quebec, Canada; <sup>27</sup>Department of Cardiology, Heart Center at University of Leipzig and Leipzig Heart Institute, Leipzig, Germany; <sup>28</sup>CardioVascular Center Frankfurt CVC, Frankfurt, Germany; <sup>29</sup>Department of Cardiovascular Surgery, Mount Sinai Health System, New York, NY, USA; <sup>30</sup>Centre for Heart Valve Innovation, St. Paul Hospital, Vancouver, British Columbia, Canada; <sup>31</sup>Department of Interventional Cardiology, Centro Cardiologico Monzino IRCCS, Milan, Italy; <sup>32</sup>Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy; and <sup>33</sup>HerzZentrum Hirslanden, Hirslanden Clinic, Zurich, Switzerland

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\* Corresponding author. E-mail: francesco.cannata@cardiologicomonzino.it

† These authors contributed equally to this work.

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## 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.<sup>1,2</sup> 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.<sup>3–5</sup>

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.<sup>6–8</sup> 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.<sup>9</sup>

Increasing severity of TR is associated with declining cardiac output,<sup>2</sup> 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.<sup>10</sup> Physiological studies, instead, have demonstrated MR worsening in response to preload augmentation, especially in the setting of LV systolic dysfunction<sup>2,6</sup>; 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.<sup>11,12</sup> 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.<sup>13,14</sup> TR and MR severity grading was assessed according to European and American guidelines using a combination of semiquantitative and quantitative measurements.<sup>7</sup> 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  $\leq 2+$ .<sup>11</sup> 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.<sup>15</sup>

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 ( $\pm$ 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  $\chi^2$  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).

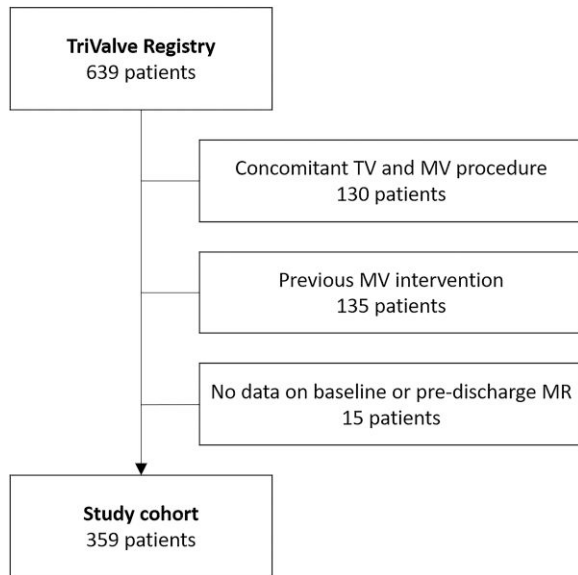
## Results

### 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)	<b>0.008</b>
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%)	<b>&lt;0.001</b>
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%)	<b>0.003</b>
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 ( $\pm 112$ )	89 ( $\pm 124$ )	84 ( $\pm 89$ )	85 ( $\pm 91$ )	0.668
2-month furosemide equivalent dose (mg)	72 ( $\pm 78$ )	76 ( $\pm 87$ )	61 ( $\pm 47$ )	77 ( $\pm 87$ )	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)	<b>&lt;0.001</b>
LVEF ≤ 30%	26 (7%)	7 (3%)	14 (13%)	5 (15%)	<b>0.001</b>
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%)	<b>0.045</b>
Left atrial volume	93 (69–126)	88 (65–116)	108 (78–144)	104 (70–125)	<b>0.017</b>
Baseline MR degree					<b>&lt;0.001</b>
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					<b>&lt;0.001</b>
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					<b>&lt;0.001</b>
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%)	<b>&lt;0.001</b>
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%)	<b>&lt;0.001</b>

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-aldosterone; 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)	<b>0.007</b>
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%)	<b>0.009</b>
Peripheral oedema	218 (76%)	111 (71%)	82 (82%)	25 (75%)	<b>0.044</b>
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%)	<b>0.023</b>
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)	<b>0.015</b>
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					<b>&lt;0.001</b>
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					<b>&lt;0.001</b>
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					

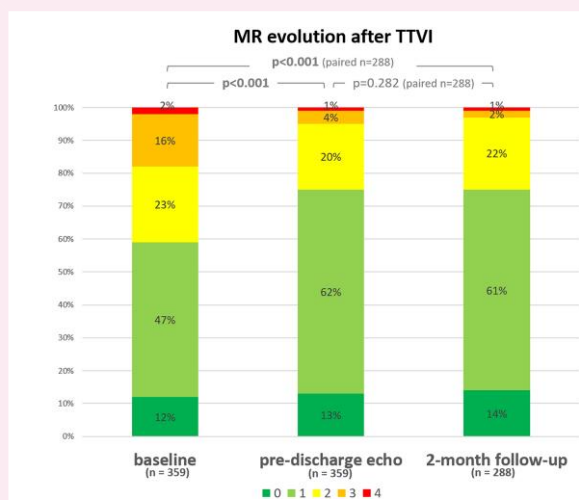
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**Table 2 Continued**

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%)	<b>0.029</b>
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%)	<b>0.037</b>

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-aldosterone; 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.<sup>4,16</sup> These interventions on the TV may trigger a cascade of hemodynamic changes involving also the left heart.<sup>17,18</sup> As a matter of fact, there exists an intricate hemodynamic interplay between TR and left heart, including the mitral valve.<sup>17</sup> Firstly, the onset of a significant TR causes right heart enlargement because of volume overload.<sup>19</sup> 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.<sup>10,20–22</sup> Hence, increased right-sided pressures impair left ventricular filling, leading to reduced left ventricular compliance.<sup>20,22</sup> 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	<b>0.25 (0.12–0.52)</b>	<b>&lt;0.001</b>	0.47 (0.20–1.08)	0.076
Annuloplasty	<b>2.90 (1.20–7.50)</b>	<b>0.020</b>	1.40 (0.39–5.06)	0.608
Orthotopic replacement	3.39 (0.87–13.20)	0.077		
Heterotopic replacement	<b>5.28 (1.50–18.5)</b>	<b>0.009</b>	<b>8.65 (2.05–36.4)</b>	<b>0.003</b>
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	<b>0.48 (0.23–0.99)</b>	<b>0.049</b>	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–aldosterone; 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<sup>10</sup> 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.<sup>22</sup> 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<sup>18</sup>, 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.<sup>23,24</sup> 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.<sup>19</sup> 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;<sup>20</sup> however, the role of cardioversion or atrial fibrillation ablation in the context of TTVI has not yet been established.

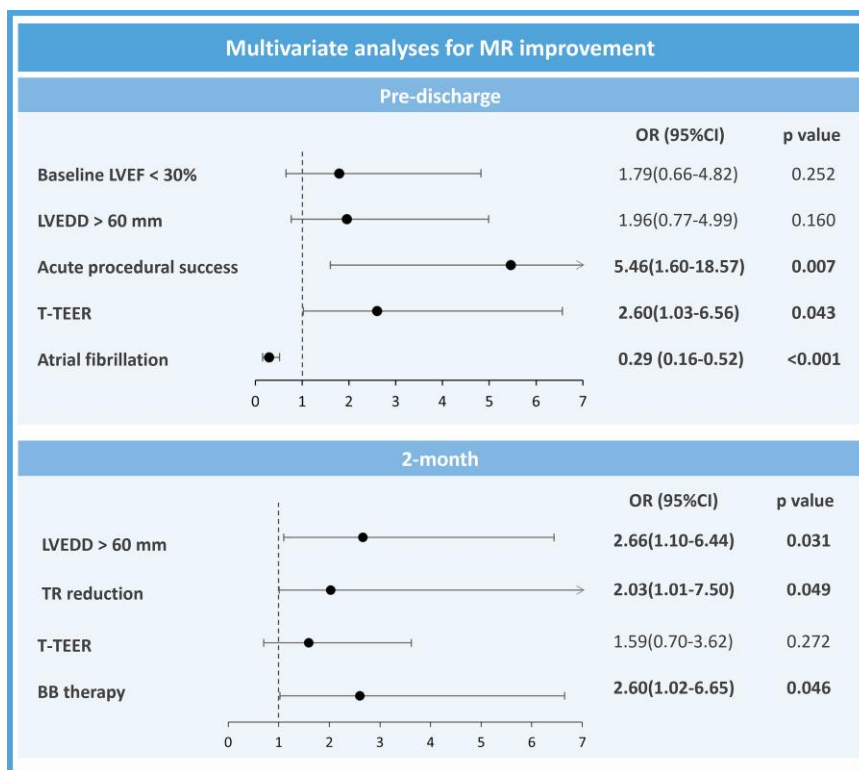


**Table 4** Continued

Characteristics	OR (95% CI)	P	OR (95% CI)	P
	Pre-discharge (n = 106)		2-month follow-up (n = 99)	
LVEDD > 60 mm	<b>2.27 (1.02–5.07)</b>	<b>0.045</b>	2.09 (0.92–4.77)	0.077
Pre-discharge LVEDD	<b>1.05 (1.02–1.08)</b>	<b>0.002</b>	<b>1.04 (1.01–1.06)</b>	<b>0.027</b>
Delta LVEDD	0.98 (0.95–1.02)	0.399	1.02 (0.98–1.06)	0.302
Baseline LVEF	<b>0.96 (0.94–0.98)</b>	<b>&lt;0.001</b>	<b>0.96 (0.94–0.98)</b>	<b>0.002</b>
Baseline LVEF < 30%	<b>3.01 (1.36–6.89)</b>	<b>0.007</b>	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	<b>0.96 (0.94–0.98)</b>	<b>&lt;0.001</b>	<b>0.97 (0.95–0.99)</b>	<b>0.005</b>
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	<b>0.46 (0.29–0.73)</b>	<b>0.001</b>	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-aldosterone; 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.





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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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