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RESEARCH ARTICLE

Evolution of tricuspid regurgitation after transcatheter edge-to-edge mitral valve repair for secondary mitral regurgitation and its impact on mortality

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Aim To evaluate short-term changes in tricuspid regurgitation (TR) after transcatheter edge-to-edge mitral valve repair (M-TEER) in secondary mitral regurgitation (SMR), their predictors and impact on mortality.

Methods and results This is a retrospective analysis of SMR patients undergoing successful M-TEER (post-procedural mitral regurgitation ≤2+) at 13 European centres. Among 503 patients evaluated 79 (interquartile range [IQR] 40–152) days after M-TEER, 173 (35%) showed ≥1 degree of TR improvement, 97 (19%) had worsening of TR, and 233 (46%) remained unchanged. Smaller baseline left atrial diameter and residual mitral regurgitation 0/1+ were independent predictors of TR ≤2+ after M-TEER. There was a significant association between TR changes and New York Heart Association class and pulmonary artery systolic pressure decrease at echocardiographic re-assessment. At a median follow-up

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of 590 (IQR 209–1103) days from short-term echocardiographic re-assessment, all-cause mortality was lower in patients with improved compared to those with unchanged/worsened TR (29.6% vs. 42.3% at 3 years; log-rank $p = 0.034$). Baseline TR severity was not associated with mortality, whereas TR 0/1+ and 2+ at short-term follow-up was associated with lower all-cause mortality compared to TR 3/4+ (30.6% and 35.6% vs. 55.6% at 3 years; $p < 0.001$). A TR ≤2+ after M-TEER was independently associated with a 42% decreased risk of mortality ($p = 0.011$).

Conclusion More than one third of patients with SMR undergoing successful M-TEER experienced an improvement in TR. Pre-procedural TR was not associated with outcome, but a TR ≤2+ at short-term follow-up was independently associated with long-term mortality. Optimal M-TEER result and a small left atrium were associated with a higher likelihood of TR ≤2+ after M-TEER.

Keywords Tricuspid regurgitation • Transcatheter edge-to-edge mitral valve repair • Mortality

Introduction

Tricuspid regurgitation (TR) is frequently observed in patients with heart failure (HF) and secondary mitral regurgitation (SMR). Prevalence of moderate to severe TR in chronic HF is about 20% regardless of left ventricular ejection fraction.[1,2] More than half of patients with HF with reduced ejection fraction and moderate to severe TR also have a significant degree (>2+) of mitral regurgitation (MR).[2]

Tricuspid regurgitation is strongly associated with mortality, which is incremental by increasing TR severity.[2,3] In patients undergoing surgical or transcatheter interventions on left-sided valvular heart disease, severe TR, if not treated, is associated with an up to two-fold increased risk of 1-year mortality.[4,5] Specific recommendations regarding the surgical treatment of TR in patients with left-sided valvular heart disease are reported.[6] Conversely, management of TR in patients undergoing percutaneous treatment of left-sided valvular heart disease remains unsettled. Importantly, TR may improve after MR treatment because of a decrease in pulmonary congestion and right ventricular afterload. However, limited evidence is available regarding changes in TR degree after transcatheter edge-to-edge mitral valve repair (M-TEER) for SMR.[7–10] Moreover, impact of TR changes on mortality and predictors of TR improvement in this setting are poorly known.[10] Since many transcatheter tricuspid valve interventions are emerging,[11,12] it would be useful to understand when a 'combined' versus 'staged' approach should be adopted in patients with concomitant MR and TR.[13]

The aim of this study was to evaluate the prognostic impact of TR changes in a large multicentre population with SMR undergoing successful M-TEER and to assess predictors of TR improvement after M-TEER.

Methods

Study population

This is a retrospective multicentre analysis including consecutive patients undergoing M-TEER with the MitraClip device (Abbott Vascular, Abbott Park, IL, USA) between December 2009 and February 2021 at 13 European centres. For the purpose of this analysis, only patients with SMR who underwent a successful M-TEER procedure (residual MR ≤2+ at discharge) and with a complete echocardiographic evaluation regarding TR degree at both baseline and short-term follow-up (between 30 and 180 days) were included. All patients were evaluated before M-TEER by a local multidisciplinary team including clinical cardiologists, interventional cardiologists, cardiac surgeons and anaesthesiologists. Pre-procedural planning and intra-procedural guidance during M-TEER was performed at each centre by expert operators.[14]

All patients gave their consent after extensive explanation of the benefits and risks of the procedure.

Data collection and definitions

Demographic, clinical, echocardiographic, procedural data, and outcomes were assessed for quality and entered into a dedicated computerized database. Echocardiographic parameters were detected at each centre by expert operators at both baseline and short-term follow-up. TR degree was assessed using a multiparametric approach according to current indications,[4] and a classification based on four degrees was used: 0 (no TR), 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe) and 4+ (severe).[15] Improved or worsened TR at short-term echocardiographic control was defined as an improvement or worsening of at least one degree of baseline TR, respectively. The population was stratified according to changes in TR degree (improved vs. unchanged or worsened) and also according to TR degree at baseline and at short-term follow-up (TR 0/1+ vs. 2+ vs. 3/4+). Clinical outcome was evaluated in terms of all-cause mortality at long-term follow-up (between short-term echocardiographic re-assessment and last patient contact).

Statistical analysis

The normal distribution of continuous variables was explored with Kolmogorov–Smirnov and the Shapiro–Wilk tests. Continuous variables following a normal distribution are reported as mean ± standard deviation (SD) and were compared using the Student's *t*-test, whereas those not following a normal distribution are presented as median and interquartile range (IQR) and were compared with the Mann–Whitney U test. Categorical variables are reported as counts and percentages and were compared using the χ^2 or Fisher exact tests, as appropriate.

Survival was assessed using the Kaplan–Meier method. Time was calculated using the date of short-term echocardiographic re-assessment as starting point and the date of last patient contact or death as final point. Differences between groups were calculated using

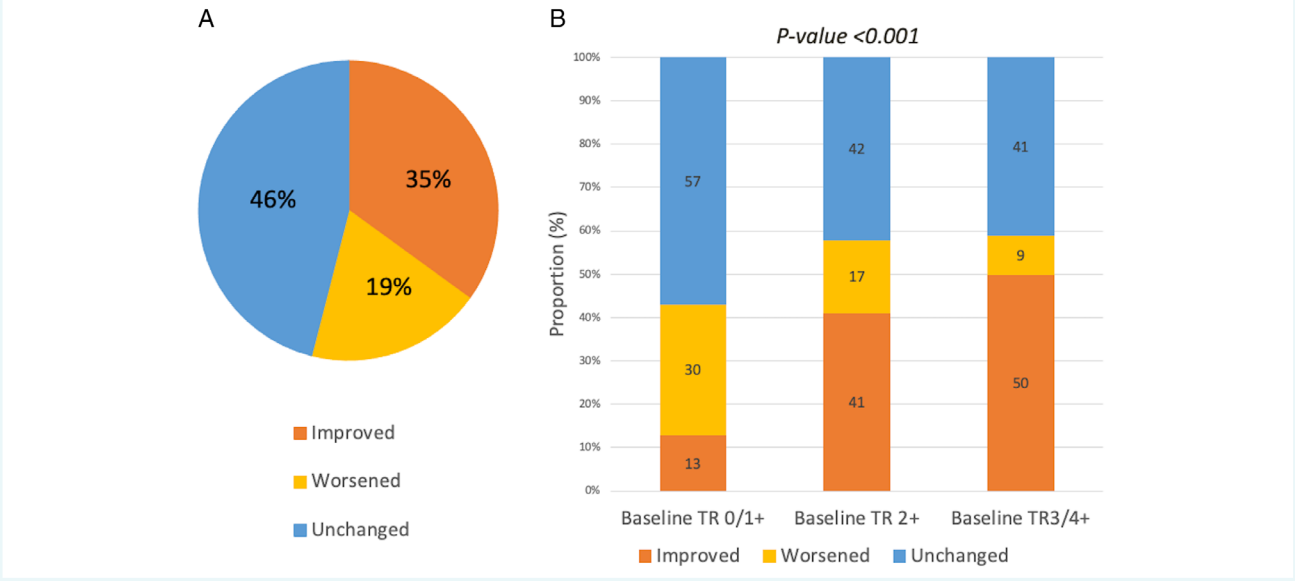

Figure 1 Evolution of tricuspid regurgitation (TR) in the overall population (*A*) and in the population stratified by baseline TR (*B*).

the log-rank test. The proportionality assumptions were checked by visual estimation after plotting the log cumulative hazard versus (log) time at follow-up after the index procedure and by applying a test for non-proportional hazards using Schoenfeld residuals, which failed to reject the null hypothesis that hazard ratio remains costant over time. A Cox regression uni- and multivariable analysis was performed to estimate the relative risk of all-cause death among the patient subgroups, which was expressed as hazard ratio (HR) and corresponding 95% confidence interval (CI). Baseline variables differently distributed ($p < 0.10$) across TR subgroups at univariate analysis were entered in two different multivariable stepwise logistic regression models in order to calculate independent predictors of TR improvement and TR ≤2+ after M-TEER. Each result was reported as odds ratio (OR) and corresponding 95% CI. Multicollinearity was tested by variance inflation factor.

For all analyses, a two-sided $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed using Stata, version 14 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics and changes in tricuspid regurgitation

Among 993 patients undergoing M-TEER during the observation period, 503 patients fulfilled inclusion criteria and were included in this study (online supplementary *Figure S1*). Comparison between patients included and excluded is reported in online supplementary *Table S1*. Among the 503 patients included, 159 (32%) had TR 0/1+, 207 (41%) had TR 2+ and 137 (27%) had TR 3/4+ at baseline. Short-term echocardiographic evaluation was performed at a median of 79 (IQR 40–152) days with 267 (53%) patients receiving echocardiography ≤90 days and 236 (47%) >90 days after successful M-TEER. At short term, TR 0/1+ was observed in 216 (43%), TR 2+ in 158 (31%) and TR 3/4+ in 129 (26%) patients. Baseline demographic, clinical and echocardiographic features stratified according to baseline TR degree and TR degree at short-term follow-up are reported in online supplementary *Tables S2* and *S3*.

An improvement of ≥1 TR degree was observed in 173 patients (35%), worsening of ≥1 TR degree was noted in 97 patients (19%), whereas TR severity remained unchanged in 233 patients (46%) (*Figure 1A*). The likelihood of TR improvement was higher among patients with baseline TR 2+ or 3/4+. On the other hand, the proportion of patients with unchanged or worsened TR was higher among those with baseline TR 0/1+ (*Figure 1B*).

Predictors of tricuspid regurgitation improvement

Baseline demographic and clinical characteristics were similar in patients with improved compared to those with unchanged or worsened TR after M-TEER except for prior cardiac surgery that was less frequent in patients who had TR improvement compared to the others (*Table 1*). With respect to the echocardiographic variables, left atrial diameter (LAD) and mitral valve annulus dimensions were lower, and pulmonary artery systolic pressure (PASP) was higher in patients with improved versus those with unchanged/worsened TR after M-TEER (*Table 2*). LAD was independently associated with the likelihood to have an improvement of ≥1 TR degree (OR 0.90; 95% CI 0.82–0.99; $p = 0.029$) or a TR ≤2+ after M-TEER (OR 0.93; 95% CI 0.88–0.98; $p = 0.012$) (*Table 3*).

Procedural data were similar between the two groups except for the rate of post-procedural MR 0/1+ that was higher in patients who had TR improvement compared to those with unchanged or worsened TR (*Table 4*). A post-procedural residual MR 2+ (vs. 0/1+) was associated with a decreased probability to have a TR ≤2+ after M-TEER (OR 0.13; 95% CI 0.05–0.40; $p < 0.001$) (*Table 3*).

Table 1 Baseline characteristics

Variables	TR unchanged/worsened (n = 330)	TR improved (n = 173)	p-value
Age (years), mean ± SD	71 ± 11	73 ± 8	0.072
Male sex, *n* (%)	243 (74)	131 (76)	0.668
Body mass index (kg/m^2), mean ± SD	26.4 ± 4.5	26.7 ± 4.8	0.584
EuroSCORE II (%), median (IQR)	5.4 (2.7–11.4)	4.9 (2.6–8.9)	0.295
Hypertension, *n* (%)	211 (64)	114 (66)	0.695
Diabetes, *n* (%)	104 (31.5)	56 (32.4)	0.841
History of atrial fibrillation, *n* (%)	172 (52.1)	80 (46.2)	0.223
Coronary artery disease, *n* (%)	157 (61.1)	82 (55)	0.251
Peripheral artery disease, *n* (%)	52 (15.8)	27 (15.6)	0.768
Chronic obstructive pulmonary disease, *n* (%)	50 (15.2)	26 (15)	1.000
Prior cardiac surgery, *n* (%)	144 (44)	58 (34)	0.035
eGFR (ml/min/1.73 m^2), mean ± SD	52 ± 23	53 ± 22	0.347
eGFR <60 ml/min/1.73 m^2, *n* (%)	221 (67.6)	108 (62.4)	0.248
Haemoglobin (g/dl), mean ± SD	11.7 ± 1.7	11.9 ± 2.5	0.710
NT-proBNP (pg/ml), median (IQR)	3594 (1720–8186)	2930 (1597–6382)	0.648
Cardiac resynchronization therapy, *n* (%)	131 (39.7)	71/172 (41.3)	0.774
Beta-blockers, *n* (%)	286 (86.7)	147 (85)	0.591
RASi, *n* (%)	236 (72)	124 (72)	0.559
Furosemide dose (mg/die), median (IQR)	80 (50–139)	75 (50–125)	0.606
NYHA class, *n* (%)			0.139
II	35 (10.6)	28 (16.2)	
III	221 (67)	114 (65.9)	
IV	74 (22.4)	31 (17.9)	

eGFR, estimated glomerular filtration rate; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin–angiotensin system inhibitor; SD, standard deviation; TR, tricuspid regurgitation.

Table 2 Baseline echocardiographic data

Variables	TR unchanged/worsened (n = 330)	TR improved (n = 173)	p-value
MR aetiology	157 (61.1)	82 (55)	0.251
MR degree, *n* (%)			0.225
3+	55 (16.7)	37 (21.4)	
4+	275 (83.3)	136 (78.6)	
Mitral valve annulus (mm), mean ± SD	38.6 ± 7.6	35.5 ± 4.6	0.001
LA diameter (mm), mean ± SD	52.1 ± 6.9	49.5 ± 5.9	0.014
LA area (cm^2), mean ± SD	32.338 ± 7.40	32.255 ± 8.475	0.933
LA volume (ml), mean ± SD	123.4 ± 52.1	124.2 ± 47.2	0.870
LVEDD (mm), mean ± SD	65.5 ± 9.8	65 ± 11	0.610
LVESD (mm), mean ± SD	52.7 ± 17.1	52.1 ± 13.2	0.761
LVEDV (ml), mean ± SD	199.5 ± 77.1	195.6 ± 66.5	0.588
LVESV (ml), mean ± SD	134.2 ± 66.7	131.6 ± 58	0.678
LVEF (%), mean ± SD	32.8 ± 10.4	32.7 ± 10	0.903
TAPSE (mm), mean ± SD	17.5 ± 3.8	17.5 ± 3.8	0.903
PASP (mmHg), mean ± SD	45.9 ± 13.5	51.9 ± 14.6	<0.001

LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Table 3 Predictors of tricuspid regurgitation ≤2+ after transcatheter edge-to-edge mitral valve repair

Variables	Bivariate		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (years)	0.99 (0.97–1.01)	0.238		
Male sex	0.77 (0.49–1.20)	0.251		
EuroSCORE II	1.00 (0.99–1.01)	0.258		
Hypertension	1.04 (0.77–1.42)	0.791		
Atrial fibrillation	0.57 (0.38–0.86)	0.007	0.92 (0.42–2.02)	0.836
Ischaemic aetiology	1.07 (0.68–1.7)	0.764		
Chronic kidney disease	0.68 (0.36–1.28)	0.234		
Cardiac resynchronization therapy	0.68 (0.45–1.02)	0.059	0.82 (0.36–1.87)	0.633
Beta-blockers	0.92 (0.51–1.65)	0.779		
RASi	1,45 (0.79–2.66)	0.226		
NYHA class IV	0.74 (0.46–1.18)	0.204		
LA diameter (mm)	0.93 (0.88–0.98)	0.005	0.93 (0.88–0.98)	0.012
LVEDV (ml)	1.00 (1.00–1.01)	0.040	1.00 (1.00–1.01)	0.469
LVEF (%)	1.01 (0.99–1.03)	0.319		
TAPSE (mm)	1.08 (1.02–1.14)	0.008	1.04 (0.93–1.16)	0.490
PASP (mmHg)	0.99 (0.98–1.01)	0.580		
MR degree post-M-TEER (2+ vs. 1+)	0.39 (0.25–0.60)	<0.001	0.13 (0.05–0.40)	<0.001
MR gradient post-M-TEER (mmHg)	1.02 (0.88–1.18)	0.809		

CI, confidence interval; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; M-TEER, transcatheter edge-to-edge mitral valve repair; NYHA, New York Heart Association; OR, odds ratio; PASP, pulmonary artery systolic pressure; RASi, renin–angiotensin system inhibitor; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Table 4 Procedural and short-term outcomes[a]

Variables	TR unchanged/worsened (*n* = 330)	TR improved (*n* = 173)	*p*-value
Number of clips, *n* (%)			0.995
1	141 (43)	74	
2	165 (50)	86	
>2	24 (7)	13	
Mitral regurgitation degree, n (%)			<0.001
0/1+	237 (72)	149 (86)	
2+	93 (28)	24 (14)	
Transmitral mean gradient (mmHg), mean ± SD	3.8 ± 2.7	3.2 ± 1.4	0.063
LVEF (%) at short-term follow-up, mean ± SD	32 ± 9	32 ± 11	0.987
Changes in LVEF (%), median (IQR)	0 (−4/ +4)	0 (−4/ +3)	0.770
TAPSE (mm) at short-term follow-up, mean ± SD	18 ± 4	18 ± 4	0.111
Changes in TAPSE (mm), median (IQR)	0 (−2/ +3)	+1 (−1/ +3)	0.131
PASP (mmHg) at short-term follow-up, mean ± SD	42 ± 13	39 ± 12	0.010
Changes in PASP (mmHg), median (IQR)	−5 (−12/ +5)	−11 (−22/−4)	<0.001
NYHA class at short-term follow-up			0.004
I	63 (19.1)	44 (25.4)	
II	192 (58.2)	112 (64.7)	
III	64 (19.4)	15 (8.7)	
IV	11 (3.3)	2 (1.2)	
Changes in NYHA class, mean ± SD	1.05 ± 0.80	1.16 ± 0.81	0.132
HF hospitalizations, *n* (%)	37 (11.2)	15 (8.7)	0.442

HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

[a]Short-term echocardiographic evaluation was performed at a median of 79 (IQR 40–152) days after transcatheter edge-to-edge mitral valve repair.

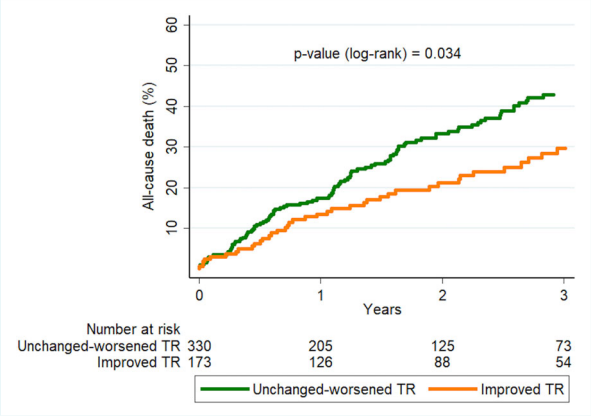

Figure 2 Cumulative incidence of all-cause death by tricuspid regurgitation (TR) evolution in the overall population.

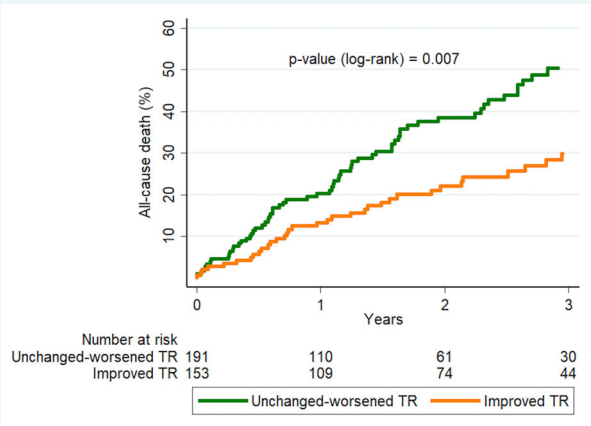

Figure 3 Cumulative incidence of all-cause death by tricuspid regurgitation (TR) evolution in patients with TR >2+ at baseline.

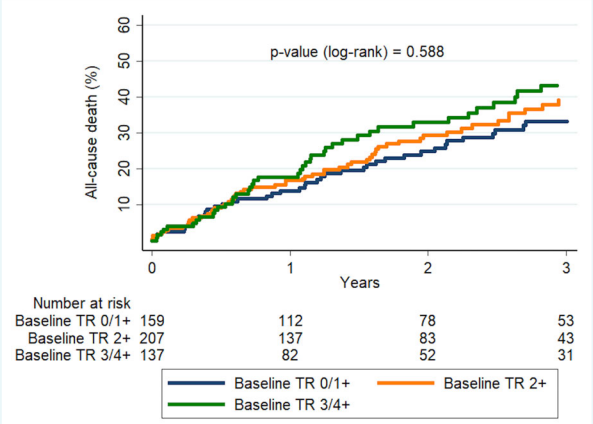

Figure 4 Cumulative incidence of all-cause death by baseline tricuspid regurgitation (TR).

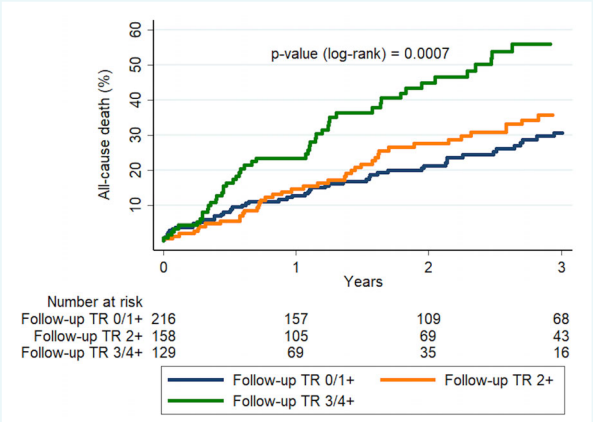

Figure 5 Cumulative incidence of all-cause death by tricuspid regurgitation (TR) at short-term follow-up.

Clinical outcomes

Improvement of TR was associated with a greater decrease in PASP values after M-TEER (*Table 4*).

There was a significant association between New York Heart Association (NYHA) class after M-TEER and TR changes at short-term evaluation (*Table 4*).

Median follow-up from short-term evaluation was 590 (IQR 209–1103) days. All-cause death occurred in 13 patients within 30 days of the short-term evaluation, in 57 patients between 30 days and 1 year, and in 104 patients after 1 year. The cumulative incidence of all-cause mortality was lower in patients with improved compared to those with unchanged/worsened TR (13.5% vs. 17.1% at 1 year and 29.6% vs. 42.3% at 3 years; log-rank $p = 0.034$) (*Figure 2*), especially in the subgroup of patients with TR ≥2+ at baseline (log-rank $p = 0.007$) (*Figure 3*). There were no significant differences in the cumulative incidence of all-cause mortality in patients with baseline TR 0/1+ versus 2+ versus 3/4+ (13.8% vs. 16.3% vs. 17.7% at 1 year and 33.1% vs. 38.9% vs. 43.1% at 3 years, respectively; log-rank $p = 0.588$) (*Figure 4*). On the other hand, patients with TR 3/4+ at short-term follow-up had a higher all-cause mortality compared to those with TR 0/1+ and TR 2+ at short-term follow-up (22.9% vs. 12.8% and 14.7% at 1 year and 55.6% vs. 30.6% and 35.6% at 3 years, respectively; log-rank $p < 0.001$) (*Figure 5*), regardless of baseline TR (*Figure 6*). At multivariable analysis for long-term mortality, age, left ventricular ejection fraction and TR ≤2+ at short-term follow-up after M-TEER (HR 0.58; 95% CI 0.38–0.88; $p = 0.011$) were independent predictors of long-term mortality. Conversely, improvement of at least one TR degree did not reach statistical significance for reduction in the relative risk of mortality after M-TEER (HR 0.73; 95% CI 0.50–1.06; $p = 0.101$) (*Table 5*).

Discussion

The main findings of the present study are as follows: (i) in more than one third of patients with SMR undergoing successful

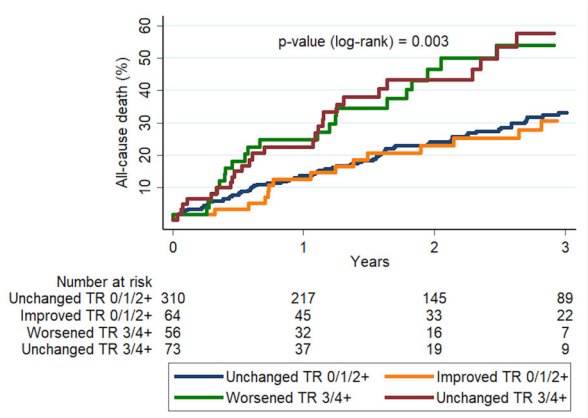

Figure 6 Cumulative incidence of all-cause death by tricuspid regurgitation (TR) evolution and according to baseline TR.

M-TEER, an improvement of at least one degree of TR is observed; (ii) post-procedural degree of MR (MR degree 0/1+ vs. 2+) and a smaller baseline LAD are associated with a greater likelihood to have a TR ≤2+ after M-TEER; (iii) an improvement in TR after M-TEER of at least one degree is associated with reduced HF symptoms and a decrease in pulmonary hypertension; and (iv) TR improvement is associated with a lower mortality compared with unchanged or worsened TR after M-TEER. However, only TR ≤2+ (vs. TR 3/4+) at short-term evaluation, regardless of baseline TR, is independently associated with a 42% reduction in the relative risk of long-term all-cause death.

Proportion of tricuspid regurgitation improvement

To the best of our knowledge, this is the largest multicentre study investigating the association between TR changes after M-TEER for SMR and mortality. In our population, 35% of patients experienced TR improvement after successful M-TEER. These results are in line with previous single-centre, smaller size, studies reporting an improvement in TR after M-TEER ranging from 23% to 41%.[7–10] The proportion of patients with SMR in these cohorts was approximately 60% and procedural success (post-procedural MR ≤2+) was >90%.

Predictors of tricuspid regurgitation improvement

Regarding the predictors of TR changes after M-TEER, we found baseline smaller LAD and MR (0/1+ vs. 2+) post-M-TEER as independently associated with TR improvement or TR ≤2+ after MR correction. In particular, each 1% increase in LAD is associated with a 7% decrease in the probability to have a TR ≤2+ after M-TEER. We can speculate that patients with a large left atrium are more likely to have an atrial disease (i.e. due to atrial fibrillation) that may contribute to TR regardless of MR. On the other hand, high LAD can be related to a long-standing mitral valve disease resulting in a lower probability of TR improvement. Of note, LAD was already reported as a strong predictor of adverse outcomes after M-TEER in the TRAnscatheter Mitral valve Interventions (TRAMI) study.[16] We also observed that a residual MR 2+ (vs. 0/1+) post-M-TEER was associated with an 87% reduced likelihood to have a TR ≤2+ at short-term follow-up. This confirms the importance to achieve optimal procedural result after M-TEER in order to derive a prognostic benefit from the procedure.[17–20]

There is only a single-centre study by Kavsur *et al.*[10] assessing predictors of TR improvement after M-TEER by a multivariable model. This study showed that atrial fibrillation, tricuspid annulus dimensions ≥34 mm and residual MR ≥2+ were associated with a reduced probability to improve TR.

Atrial fibrillation was not selected in our multivariable model and no collinearity was observed with other variables such as LAD. On the other hand, left atrial dimension was not reported in the multivariable analysis by Kavsur *et al.*,[10] where atrial fibrillation may

Table 5 Multivariable analysis for all-cause mortality

Variables	Model 1[a]		Model 2[b]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)	1.05 (1.02–1.07)	<0.001	1.05 (1.03–1.08)	<0.001
Ischaemic aetiology	1.26 (0.85–1.86)	0.257	1.32 (0.89–1.94)	0.165
NYHA class IV	1.43 (0.96–2.12)	0.077	1.46 (0.99–2.17)	0.057
LVEF (%)	0.96 (0.94–0.98)	0.001	0.96 (0.94–0.98)	0.001
TAPSE (mm)	0.96 (0.91–1.01)	0.143	0.97 (0.92–1.03)	0.315
MR degree post-M-TEER (2+ vs. 1+)	1.33 (0.87–2.05)	0.189	1.18 (0.75–1.87)	0.465
TR improvement (vs. unchanged or worsened)	0.73 (0.50–1.06)	0.101	–	
TR ≤2+ (vs. 3/4+) at short-term follow-up	–		0.58 (0.38–0.88)	0.011

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; M-TEER, transcatheter edge-to-edge mitral valve repair; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

[a]To test the impact of TR improvement after adjustment for variables differently distributed at univariate analysis (online supplementary *Table S4*).

[b]To test the impact of TR ≤2+ at short term after adjustment for variables differently distributed at univariate analysis (online supplementary *Table S4*).

be considered as a surrogate of left atrial enlargement because strongly correlated.

Tricuspid annulus dimension is a validated parameter for the indication for tricuspid valve surgery in patients with left-sided valvular heart disease.[6] Unfortunately, tricuspid annulus dimension was not available in our cohort. Even in this case, an excessive dilatation of the tricuspid annulus could be considered as a surrogate of more advanced cardiac dysfunction and/or atrial disease.

Finally, the role of reaching MR 0/1+ after M-TEER is even more pronounced in our study compared with that by Kavsur *et al.*[10] since the control group is MR 2+ rather than MR ≥2+.

Association between tricuspid regurgitation improvement and symptoms

Two previous small studies reported an association between TR improvement and PASP reduction after M-TEER.[7,8] These data are confirmed by our study, and likely due to the unloading effect of MR correction on the pulmonary circulation. In a single-centre population undergoing M-TEER, Geyer *et al.*[9] reported a higher proportion of NYHA improvement in patients with TR reduction versus no TR reduction. Similarly, we observed a significant association between NYHA class and TR reduction after M-TEER.

Association between tricuspid regurgitation changes and mortality

All-cause mortality in our population was significantly lower in patients with improved TR compared to those with unchanged/worsened TR. Geyer *et al.*[9] observed similar results in the subgroup of patients with SMR ($n = 185$). Another small study showed a lower survival rate in 35 patients with TR improvement compared to 42 patients with no TR improvement after M-TEER.[21] Interestingly, we observed that TR degree at a short-term evaluation (median 79 days) after M-TEER is one of the strongest predictors of mortality. In particular, TR 3/4+ after M-TEER, either worsened or unchanged compared with baseline, is associated with a higher risk of all-cause mortality even after adjustment for possible confounders. Conversely, in our population TR degree at baseline was not associated with mortality. This is in line with an analysis from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial evaluating the role of baseline TR on outcomes. Baseline TR did not affect the impact of intervention (MitraClip and optimal medical therapy vs. medical therapy alone) on outcomes. However, TR ≥2+ at baseline was associated with poorer outcomes, compared with TR 0/1+, in the conservative arm but not in the interventional arm.[22] Of note, in the COAPT study, procedural success was extremely high and severe TR was an exclusion criterion.[23–25] Our results are also in line with the Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation (GRASP) registry, where baseline TR ≥2+ was associated with a lower survival free from cardiovascular events compared to TR 0/1+; however, no differences between groups were observed in all-cause mortality.[26] Conversely, in the TRAMI registry, patients with secondary MR and TR ≥2+ at baseline had a lower survival compared to those with TR 0/1+.[27] Discrepancy between TRAMI and our results can be due to the higher selection of our population including only patients with an available short-term follow-up evaluation, thus alive at a median of 79 days, and who received a successful M-TEER (post-procedural MR ≤2+). Nevertheless, considering that TR degree changed after M-TEER in more than half of patients, it is reasonable that TR degree after M-TEER has a greater impact on outcome compared with baseline TR.

The independent predictive value for higher mortality of age and left ventricular ejection fraction, in addition to TR 3/4 +, in our patients is in line with previous studies.[28–30]

Combined versus staged approach in patients with mitral and tricuspid regurgitation

Our results show that the probability to have regression of TR after M-TEER is higher in patients with small left atria and optimal procedural result. However, since almost half of patients with baseline TR >2+ improved to TR ≤2+ after M-TEER, this study suggests that a strategy based on short-term re-evaluation after M-TEER, followed by a staged transcatheter tricuspid valve procedure, if needed, might be more appropriate than a default single transcatheter procedure on both valves.

Limitations

Several limitations should be acknowledged. First, this is a retrospective observational study, therefore all the associations reported need to be interpreted as hypothesis-generating only. Although multivariable analyses were performed, many unknown variables may have affected our results. Second, despite echocardiographic data were analysed at each centre by expert operators, a core laboratory for the independent evaluation of the images was lacking. Quantitative and semiqualitative parameters to assess TR degree (effective regurgitant orifice area, regurgitant volume, vena contracta, hepatic vein flow) were not available. Moreover, the new classification based on five TR degrees was not used because not available when the enrolment started. The limitations of the assessment of left atrial function through LAD, as a predictor of TR evolution after M-TEER, should also be considered as this parameter has limited accuracy and reproducibility.

Many variables that could affect TR severity and its improvement after M-TEER were not collected in this large multicentre study. Of note, data on systemic blood pressure and heart rate, as well as the presence of pacemaker lead at baseline (we only have information about cardiac resynchronization therapy) were lacking. In addition, no data were available on tricuspid annulus dimensions, right chamber dimensions, post-procedural left atrial pressure and residual interatrial shunt as well as on changes in fluid status, body weight or medical therapies after discharge. With respect to clinical events, although no surgical or percutaneous intervention

on tricuspid or mitral valve occurred after M-TEER, detailed data regarding other events such as pacemaker implantations or new onset of atrial fibrillation, were lacking. Data regarding quality of life, functional capacity and cardiac biomarkers at baseline and follow-up were also lacking. Finally, because of the inclusion criteria, our study does not apply to patients with SMR and residual MR >2+ after M-TEER and the best strategy to manage residual TR remains unclear in these patients.

Conclusions

Improvement in TR occurs in more than one-third of patients undergoing successful M-TEER for SMR. Residual MR 2+ (vs. 1+) and increased LAD are associated with a reduced likelihood to have TR ≤2+ after M-TEER. A TR ≤2+ at short-term follow-up after M-TEER was associated with a lower risk of mortality regardless of baseline TR.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: M.A. received speaker fees from Abbott Vascular and Medtronic. R.E.L. is consultant for Abbott Vascular, Boston Scientific and Edwards Lifesciences. G.S. received personal fees Novartis, Bayer, AstraZeneca, Boston Scientific, Vifor Pharma, Menarini, Akcea Therapeutics. F.B. received speaker fees from Abbott Vascular. A.S.P. is consultant for Abbott Vascular, Boston and Medtronic. I.P. is Proctor for Abbott Vascular. L.N.F. is proctor for Abbott and received consultant fees from Abbott and Edwards Lifesciences. M.M. received consulting honoraria for participation in steering committees or advisory boards or for speeches from Abbott Vascular, Amgen, AstraZeneca, Bayer, Edwards, Fresenius, Novartis, and Servier. All other authors have nothing to disclose.

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