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Predictors and prognostic relevance of tricuspid alterations in patients undergoing transcatheter edge-to-edge mitral valve repair

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KEYWORDS

- mitral regurgitation
- mitral valve repair
- tricuspid disease

Abstract

Background: Mitral valve repair may lead to alterations of tricuspid regurgitation (TR).

Aims: We aimed to investigate alterations, predictors and prognostic relevance of TR evolution in a large-scale multicentre population of patients undergoing transcatheter mitral valve repair (TMVR) via the MitraClip.

Methods: In total, we included 531 TMVR patients with at least one available follow-up echocardiography. TR improvement was defined as a TR ≥II at baseline, which showed a decline of at least one TR categorisation.

Results: Distribution of preprocedural TR severity was TR 0/I 41% (220/531), TR II 39% (209/531) and TR ≥III 19% (102/531), respectively. Follow-up echocardiography was at 308±187 days. TR severity improved to TR 0/I 49% (259/531), TR II 35% (183/531) and TR III 17% (89/531), p=0.003. Out of 311 patients with TR ≥II at baseline, 41% (127/311) showed TR improvement. Atrial fibrillation (AF), residual mitral regurgitation ≥II (rMR) and tricuspid annular diameter (TAD) remained variables which prevented TR improvement (odds ratio 0.49 [0.29-0.84], 0.47 [0.27-0.81] and 0.97 [0.93-0.997], respectively). TR improvement was associated with better event-free survival regarding post-procedural heart failure hospitalisation (HHF) (hazard ratio 0.6 [0.38-0.94]). The main changes of TR severity occurred within 3 months post TMVR (p=0.006), while there were only minor TR changes between 3 and 12 months of follow-up (p=0.813).

Conclusions: TR improvement was frequent after TMVR. Predictors preventing TR improvement were AF, post-procedural rMR, and TAD. Furthermore, TR improvement was an early phenomenon occurring primarily within the first three months post TMVR and served as a suitable marker of reduced HHF.

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Abbreviations

AF	atrial fibrillation
HHF	heart failure hospitalisation
MR	mitral regurgitation
rMR	residual mitral regurgitation (after TMVR)
TAD	tricuspid annular diameter
TMVR	transcatheter mitral valve repair
TR	tricuspid regurgitation
TTVR	transcatheter tricuspid valve repair

Introduction

Transcatheter mitral valve repair (TMVR) represents a minimally invasive therapeutic option in selected patients with clinically relevant mitral regurgitation (MR) and increased surgical risk[1,2]. Among different TMVR techniques and devices, the edge-to-edge repair via MitraClip® (Abbott Vascular, Santa Clara, CA, USA) implantation is of particular interest, representing a safe procedure with a high technical success rate[3].

Tricuspid regurgitation (TR) is frequently caused by left-sided heart disease[4]. MR can lead to pulmonary hypertension and right ventricular afterload which then results in leaflet malcoaptation and TR[5]. Hence, TR is a frequent comorbidity in patients with MR[6]. Consecutively, MR reduction via TMVR might lead to an improvement of concomitant TR; however, there is a lack of large-scale data regarding this issue[7-10] which is of special interest against the background of emerging transcatheter tricuspid valve repair (TTVR) procedures[11,12]. Predictors of TR improvement could help in the decision making concerning concurrent transcatheter mitral and tricuspid repair.

In the present large-scale multicentre study, we investigated time-dependent alterations of TR in patients after TMVR, and assessed predictors preventing TR improvement. Moreover, we aimed to calculate the cut-off value of tricuspid annular diameter (TAD) associated with low TR improvement post TMVR. Lastly, we analysed whether TR improvement and tricuspid annular dilatation correlates with rates of post-procedural heart failure hospitalisation (HHF).

Methods

STUDY COHORT

In total, we included data of 531 patients with available baseline and follow-up echocardiography who underwent TMVR in the Heart Failure Network Rhineland (University Hospitals Bonn, Cologne, Düsseldorf) from August 2010 to September 2018, and received at least one MitraClip. All procedures were performed with the MitraClip system. Patients agreed to participate in our registry which was approved by the ethics committee of each individual centre in accordance with the Declaration of Helsinki. Echocardiographic data were evaluated according to the institutional practice of the treatment centre. MR severity was categorised into three grades as I (mild), II (moderate), and III (severe) according to current guidelines[13]. Assessment of TR severity was conducted as recommended by current guidelines[14], and TR severity was categorised as none/mild (0/I) versus moderate (II) versus severe (≥III) TR.

FOLLOW-UP DATA

After the MitraClip procedure, follow-up was monitored at regular clinic visits, and by telephone calls to the referring cardiologist, the general practitioner or the patients themselves. As clinical outcome parameter we determined the first readmission for heart failure within two-year follow-up after TMVR (mean available follow-up was 766±562 days). For the assessment of TR evolution after MitraClip implantation in the mitral valve, 485 echocardiographic controls were investigated at 3-month follow-up and 392 echocardiographic controls were evaluated at 12-month follow-up. Follow-up echocardiography was defined as the 12-month echocardiography and supplanted by the 3-month in patients with missing 12-month control. TR improvement was defined as a TR ≥II at baseline, which showed a decline of TR categorisation (e.g., moderate TR to none/mild TR).

STATISTICAL ANALYSIS

Normal distribution of variables was tested with the use of the Kolmogorov-Smirnov test. For comparison of two groups and continuous variables, the Student's t-test, Mann-Whitney U test, and Wilcoxon test were used. When assessing more than two groups, ANOVA or the Kruskal-Wallis test was performed for continuous variables. For categorical variables, the chi-square test was performed. The McNemar test was used for paired variables. Event-free survival rates and statistical differences were obtained by the Kaplan-Meier method and the log-rank test. Cox regression analysis was used to assess the association between parameters and event-free survival. Logistic regression analysis was performed to identify variables which were associated with TR improvement. For the multivariable analysis, we included parameters which showed a difference with $p<0.100$ in the baseline characteristics and had a significant predictive value in the univariable test. Best cut-off value was calculated via the receiver operating characteristic with the highest area under the curve. A p-value of <0.05 was considered to be statistically significant. Statistical analysis was performed with SPSS software, Version 24.0.0.0 (IBM Corp., Armonk, NY, USA).

Results

STUDY POPULATION

A total of 531 patients who underwent TMVR with available follow-up echocardiography were included in the final analysis. Mean time of the follow-up echocardiography was 308±187 days. Mean age of the patient cohort was 76.7±9.0 years; 215 (41%) were female. The patient cohort had high surgical risk with an increased median logistic EuroSCORE of 16% (9-29%). Aetiology of MR was primary in 184 (35%) patients and secondary in 347 (65%) patients. Post-procedural residual MR (rMR) ≥II was prevalent in 32% (171/525) of patients, while post-procedural MR >II was present in 6% (32/525) of patients. Mean number of implanted clips was 1.47±0.6.

TRICUSPID REGURGITATION DYNAMICS AFTER TMVR

At baseline, 41% (220/531) of patients had TR 0/I, while 39% (209/531) of patients had TR II, and 19% (102/531) of patients

had TR ≥III **(Figure 1A)**. Baseline patient characteristics according to TR severity are summarised in **Table 1**. Assessment of follow-up echocardiography revealed a significant change in TR distribution after TMVR – 49% (259/531), 35% (183/531) and 17% (89/531) of patients with TR 0/I, II and ≥III, respectively (p=0.003) **(Figure 1A)**. In patients with TR 0/I at baseline, 24% (53/220) and 4% (9/220) of patients showed a TR worsening to TR II and TR ≥III, respectively **(Figure 1B)**. In patients with TR II at baseline, 42% (88/209) of patients had a TR improvement to TR 0/I, while in 14% (30/209) of cases TR deteriorated to TR ≥III **(Figure 1C)**. Patients with TR ≥III at baseline had a TR improvement to TR 0/I and TR II in 38% (39/102) and 13% (13/102) of cases, respectively **(Figure 1D)**.

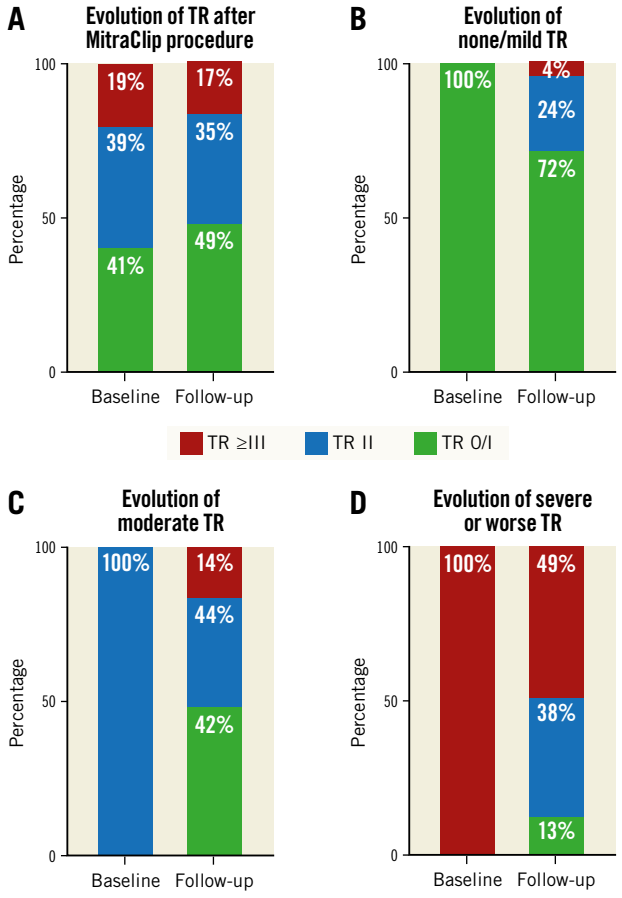

Figure 1. *Evolution of tricuspid regurgitation after MitraClip procedure. A) The percentage of tricuspid regurgitation (TR) severity changed significantly after transcatheter mitral valve repair (TMVR) (p=0.003). B) - D) Changes of TR after TMVR are shown for each of the TR groups separately.*

Table 1. Baseline characteristics according to tricuspid regurgitation.

	None/mild TR	Moderate TR	≥Severe TR	*p*-value
Patients, n	220 (41%)	209 (39%)	102 (19%)	
Clinical characteristics				
Age, years	78 (72-82)	78 (74-83)	78 (74-84)	0.355
Female gender	83 (38%)	86 (41%)	46 (45%)	0.442
BMI, kg/m²	26 (24-29)	26 (23-29)	24 (22-27)	**0.010**
Log EuroSCORE, %	15 (8-28)	16 (9-28)	17 (8-28)	0.853
Diabetes	56 (26%)	64 (31%)	25 (25%)	0.379
Arterial hypertension	185 (84%)	169 (81%)	84 (82%)	0.679
Prior stroke	23 (11%)	36 (17%)	12 (12%)	0.104
COPD	45 (21%)	37 (18%)	22 (22%)	0.660
Coronary artery disease	146 (66%)	138 (66%)	58 (57%)	0.208
Prior CABG	62 (28%)	63 (30%)	29 (28%)	0.896
Prior valvular surgery	31 (14%)	26 (12%)	10 (10%)	0.557
Atrial fibrillation	121 (55%)	135 (65%)	85 (83%)	**<0.001**
Pacemaker/ICD/CRT	77 (35%)	83 (40%)	48 (47%)	0.117
NYHA Class >II	176 (80%)	184 (88%)	90 (88%)	**0.038**
Carotid stenosis	48 (22%)	60 (29%)	28 (28%)	0.247
Echocardiographic data				
Functional MR	141 (64%)	139 (67%)	67 (66%)	0.868
LA volume, ml	91 (74-120)	100 (80-138)	109 (80-141)	**0.039**
LVEF, %	45 (32-56)	41 (31-55)	45 (31-59)	0.433
LVEDV	143 (107-189)	138 (107-186)	114 (79-171)	**0.003**
TAPSE	19 (16-22)	17 (15-22)	17 (14-20)	**0.006**
Systolic PAP, mmHg	43 (32-54)	52 (42-63)	48 (38-60)	**<0.001**
Tricuspid anulus, mm	33 (29-38)	36 (31-40)	40 (34-47)	**<0.001**
RA area, cm²	21 (16-26)	24 (19-30)	30 (24-36)	**<0.001**
Laboratory assessment				
NT-proBNP, pg/mL	2,097 (1,006-4,273)	3,260 (1,735-6,217)	3,093 (1,807-6,757)	**<0.001**
GFR, ml/min	51 (38-66)	50 (37-63)	48 (34-60)	0.381
Haemoglobin, g/dl	12.5 (11.1-13.7)	12.1 (11.0-13.3)	12.0 (10.6-13.3)	**0.014**

Values are n (%), or median (interquartile range). A *p*-value <0.05 was considered significant (bold). BMI: body mass index; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; GFR: glomerular filtration rate; ICD: implantable cardioverter defibrillator; LA: left atrial; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association; PAP: pulmonary artery pressure; RA: right atrial; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation

TR ALTERATION IS AN EARLY PHENOMENON

Next, we focused on the timing of temporal TR changes post TMVR procedure. For this analysis we included only patients with available 3-month and 12-month echocardiography (n=346), hence 165 patients with one missing follow-up echocardiography were excluded. Comparing preprocedural and 3-month data, proportions of TR 0/I, II, and ≥III varied significantly (41% [143/346] vs 41% [141/346] vs 18% [62/346], and 49% [171/346] vs 35% [122/346] vs 15% [53/346], respectively; p=0.006), while the TR distributions did not change comparing 3-month and 12-month data (49% [171/346] vs 35% [122/346] vs 15% [53/346], and 51% [176/346] vs 33% [115/346] vs 16% [55/346], respectively; p=0.813) **(Supplementary Figure 1)**. Overall, 91% (485/531) of patients had a 3-month and 74% (392/531) of patients had a 12-month available echocardiography. The evolution of TR in different subgroups according to available echocardiography is summarised in **Supplementary Table 1**.

TRICUSPID ANNULUS DIAMETER (TAD) AFTER TMVR

Follow-up TAD was available in 441 of 531 patients. In total, there was no significant change in median TAD comparing baseline and follow-up (35.9±7.5 vs 35.9±7.5 mm; p=0.949). Moreover, the median difference in tricuspid diameter at baseline and follow-up was 0 mm (-3.5 mm to 4 mm). However, in 49% (218/441) of cases TAD declined after TMVR. TR improvement tended to be more frequent in patients with a decline in TAD (58% vs 42%, p=0.052).

ATRIAL FIBRILLATION (AF), RESIDUAL MR (rMR) AND TAD PREVENT TR IMPROVEMENT

Out of 311 patients with moderate or worse TR, 41% (127/311) revealed a TR improvement at follow-up. Baseline characteristics according to TR improvement are shown in **Supplementary Table 2**. Patients with TR improvement had a lower median TAD (35 mm [31-40 mm] vs 37 mm [33-43 mm]; p=0.013), lower median NT-proBNP (2,991 pg/mL [1,868-6,385 pg/mL] vs 3,302 pg/mL [1,776-6,461 pg/mL]; p<0.001), and a lower prevalence of AF (60% vs 78%; p<0.001). Moreover, rMR ≥II at discharge was more frequent in patients without TR improvement (39% vs 24%; p=0.005). Parameters which showed a difference with a p-value <0.100 were tested for their predictive ability regarding TR improvement by logistic regression analysis **(Table 2)**. In the multivariable analysis, AF (odds ratio [OR] 0.49, 95% confidence interval [CI]: 0.29-0.84; p=0.009), rMR ≥II at discharge (OR 0.47, 95% CI: 0.27-0.81; p=0.007) and TAD (OR 0.97, 95% CI: 0.93-0.997, per 1 mm increase; p=0.032) remained predictive parameters associated with a reduced probability of TR improvement. Missing values were excluded from the multivariable analysis, which led to the inclusion of 289/311 (93%) patients. The best predictive TAD cut-off value was for a diameter ≥34 mm. Using tricuspid annular dilatation (TAD ≥34 mm) instead of TAD, univariable regression revealed an OR of 0.40 (95% CI: 0.24-0.68; p=0.001) regarding TR improvement. Repeating multivariable analysis with tricuspid annular dilatation instead of TAD showed an OR of 0.44 (95% CI: 0.25-0.76; p=0.003) **(Table 2)**. Results for the other parameters were similar to the first multivariable model. At baseline, the subgroup of TR ≥II and a TAD ≥34 mm included 189 patients. Of these, 35% (66/189) of patients showed TR improvement of at least one grade during follow-up. However, the majority of 75% (141/189) of patients still had a TR ≥II (84 patients with TR II, 57 patients with TR III), retaining a possible TR treatment indication. In contrast, the subgroup of TR ≥II with a TAD <34 mm included 101 patients. Here, more than half (exactly 54% [54/101] of patients) had a TR improvement at follow-up, with 51/101 (50%) still having a TR ≥II at follow-up (36/101 patients with TR II, 15 patients with TR III) **(Figure 2)**.

Analysis of heart failure medication for patients with available 3-month data (n=441) showed that, comparing baseline and 3-month data, medication with a beta-blocker (88% vs 91%; p=0.044) and diuretics (88% vs 93%; p=0.003) increased. Comparing the frequencies of these medications at 3 and 12 months did not show significant changes (n=328). Sub-analyses of changes in medication and daily doses are summarised in **Supplementary Table 3**.

HHF AFTER TMVR

Including patients with TR ≥II at baseline, Kaplan-Meier curve analysis and the log-rank test showed that TR improvement was associated with a lower rate of HHF (27% [33/124] vs 37% [68/183], log-rank test p=0.042) **(Figure 3A)**. Multivariable Cox regression analysis revealed that TR improvement had a hazard ratio (HR) of 0.6 (95% CI: 0.38-0.94; p=0.025) regarding readmission for heart failure after TMVR **(Supplementary Table 4)**. Moreover, patients with a tricuspid annular dilatation (defined as a tricuspid diameter ≥34 mm) at follow-up had a significantly higher rate of HHF (37% [100/270] vs 23% [41/177]; log-rank

Table 2. Predictors of TR improvement.

	TR improvement			
	Univariable model		Multivariable model	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Atrial fibrillation (n=311/311)	0.41 (0.25-0.68)	**0.001**	0.49 (0.29-0.84)	**0.009**
Functional MR (n=311/311)	1.52 (0.93-2.47)	0.094		
LVEF, per % increase (n=308/311)	0.99 (0.97-0.999)	**0.040**	0.99 (0.97-1.003)	0.101
LVEDV, per ml increase (n=268/311)	1.003 (0.999-1.007)	0.096		
Tricuspid anulus, per mm increase (290/311)	0.96 (0.94-0.99)	**0.018**	0.97 (0.93-0.997)	**0.032**
RA area, per cm² increase (n=302/311)	0.99 (0.97-1.007)	0.199		
Residual MR ≥II at discharge (n=310/311)	0.49 (0.29-0.81)	**0.005**	0.47 (0.27-0.81)	**0.007**
NT-proBNP, per pg/mL increase (n=269/311)	1 (1-1.00004)	0.333		
Haemoglobin, per g/dl increase (n=311/311)	1.11 (0.97-1.25)	0.121		
Diuretic medication (n=311/311)	1.58 (0.75-3.4)	0.232		
Tricuspid annular dilatation (≥34 mm) (n=290/311)	0.40 (0.24-0.68)	**0.001**	0.44 (0.25-0.76)	**0.003**

A *p*-value <0.05 was considered statistically significant (bold). LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; RA: right atrial

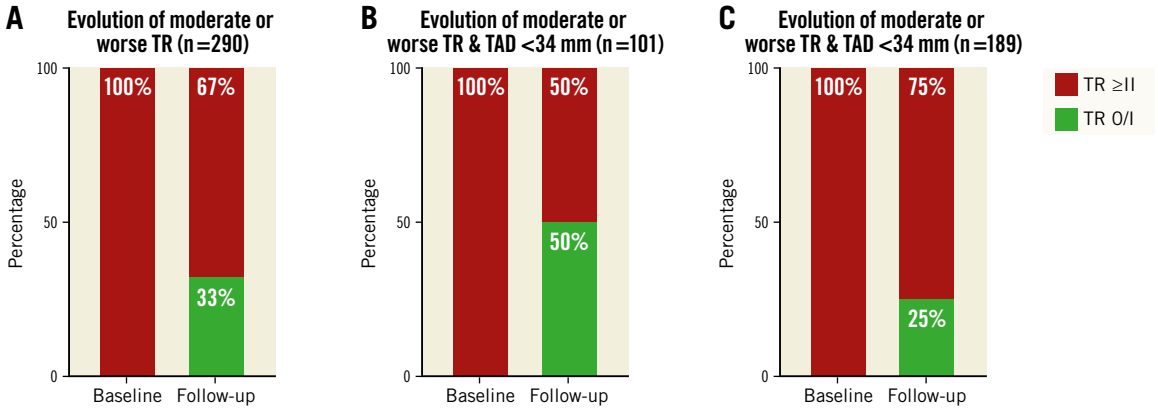

Figure 2. *Evolution of moderate or worse tricuspid regurgitation (TR) characterised by differences in tricuspid annular diameter (TAD). In the subgroup analysis of patients with TR ≥II, persistent TR ≥II remained in 67% of patients (A) after TMVR. Characterised by preprocedural TAD <34 mm (B) versus ≥34 mm (C), persistent TR ≥II distribution was 25% versus 50%, respectively.*

test p=0.001) **(Figure 3B)**. **Supplementary Table 5** summarises the baseline characteristics according to the presence of tricuspid annular dilatation at follow-up. Accordingly, parameters were tested in the univariable and multivariable Cox regression analysis **(Supplementary Table 6)**, which revealed that a tricuspid annular dilatation at follow-up was associated with a 56% increased hazard (95% CI: 6-229%; p=0.023) for an HHF after TMVR.

Discussion

In the present study, we investigated the post-procedural alterations of TR as well as predictors preventing TR improvement in patients undergoing TMVR with the MitraClip system. In this large-scale multicentre cohort, TR distribution changed significantly in patients after TMVR (p=0.003). Moreover, our results indicate that TR alterations post TMVR are an early phenomenon within the first 3 months, while there were no significant TR alterations between 3 and 12 months. Improvement of TR was observed in approximately half of the patients with moderate or worse TR at baseline. Moreover, rates of post-procedural HHF were lower in patients who showed TR improvement post TMVR. Of note, TAD served as one of three sensitive markers associated with reduced incidence of TR improvement in univariable and multivariable analysis. Therefore, TAD at baseline might be a crucial new marker helpful in terms of simultaneous transcatheter mitral and tricuspid valve repair versus TMVR-first and re-evaluate TR during follow-up. A 1 mm increase in TAD was associated with a 3% reduced probability of TR improvement. Moreover, tricuspid annular dilatation (≥34 mm) had a 0.44-fold (95% CI: 0.25-0.76) chance of TR improvement. Overall, the median TAD did not change during follow-up. Lastly, TR improvement and TAD (particularly <34 mm) at follow-up were markers associated with lower rates of post-procedural HHF.

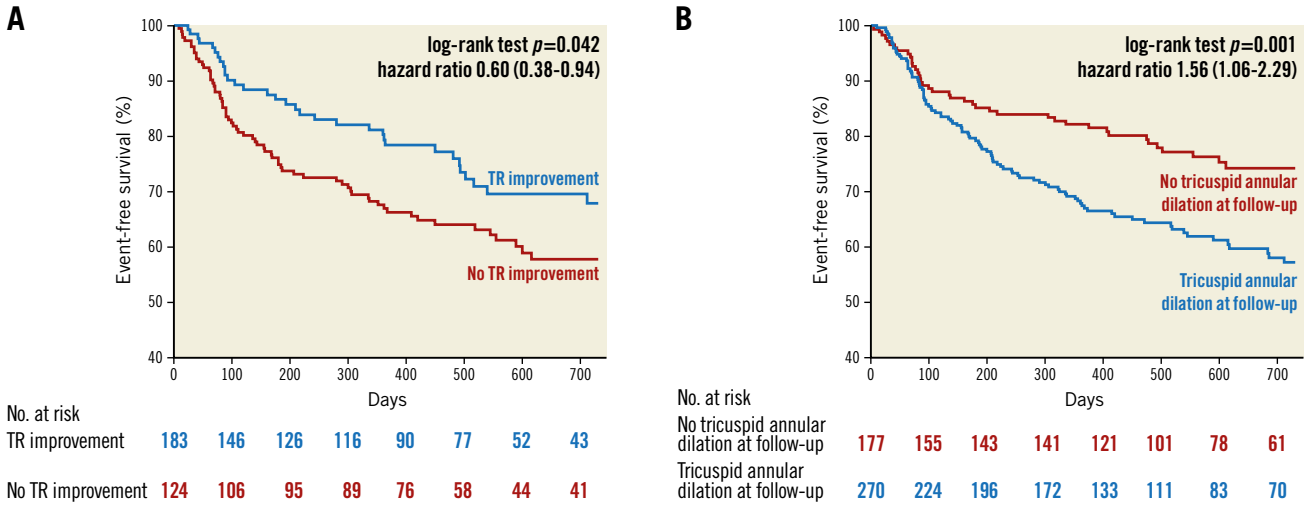

Figure 3. *Association of TR improvement and tricuspid annular dilatation with cardiac hospitalisation. A) Patients without tricuspid regurgitation (TR) improvement had lower rates of event-free survival in terms of hospitalisation for heart failure. B) Tricuspid annular dilatation at follow-up was also associated with heart failure hospitalisation.*

TRICUSPID REGURGITATION ALTERATIONS AFTER TMVR

Prior studies regarding this topic showed that TR has a predictive value regarding survival rates after TMVR[7,10,15,16], countering the idea of TR being a silent bystander. Ultimately, improvement of TR in this patient cohort represents a goal worth aiming for. Changes of TR grade were quite frequent. The proportion of none/mild TR increased, while the proportion of moderate or worse TR decreased, indicating an overall beneficial impact of TMVR on TR evolution. Medical treatment of TR involves diuretics which decrease volume overload. In our extensive analysis of heart failure medication, there was a clinically mild but statistically significant increase in diuretics with 91% to 96% or 88% to 95% at baseline and three months of follow-up within the group of TR II or no TR improvement, respectively. Therefore, this sub-analysis indicates that the changes in medication were from the clinical perspective mild and did not explain the TR improvement we observed. Focusing on the temporal changes of TR alterations, relevant changes occurred within the first 3 months post TMVR, while there were no significant differences comparing 3-month and 12-month TR. This supports the idea that the majority of TR improvement occurs during the first 3 months, and not thereafter. However, this has to be proven in a prospective randomised clinical trial with an appropriate sample size.

TR IMPROVEMENT DUE TO TMVR AND THE ROLE OF TAD

For decades the idea has persisted that tricuspid pathology is spontaneously regressive once left-sided heart lesions have been successfully treated. Today, recommendations favour concurrent tricuspid valve surgery at the time of left-sided valve repair[2]. However, modern percutaneous approaches are considered to be safe even in reinterventions due to their minimally invasive character. Moreover, transcatheter approaches for isolated severe MR, TR or simultaneous repair of severe MR and TR represent novel and innovative treatment options in our patients[11,12,17]. Conclusively, in contrast to surgical repair for transcatheter therapy, a wait-and-see approach may be feasible regarding TR patients undergoing mitral valve repair. Optimally, if there is an improvement of TR post TMVR, the additional risks and costs of TR repair might be avoided. The present study indicates that TMVR may lead to an improvement of TR. Here, 41% of patients with moderate or worse TR showed a marked TR reduction during follow-up. However, for the total cohort, a proportion of patients with severe or worse TR experienced only a minor decline from 19% to 17%. Especially in patients with a TAD ≥34 mm, TR improvement was less frequent compared to in patients with a TAD <34 mm (35% vs 54%, respectively). Moreover, persistent TR ≥II was more frequent in patients with a TAD ≥34 mm than in patients with a TAD <34 mm (75% vs 50%, respectively) **(Figure 2B, Figure 2C)**. Thus, TAD ≥34 mm might represent a relevant criterion to argue for immediate treatment of concomitant tricuspid valve disease. In surgical treatment of TR, TAD already has a significant role within the current guidelines, where TR surgery should be considered in patients with mild to moderate TR undergoing left-sided valve surgery with a TAD of ≥40 mm[1]. This concept could be of value in interventional TR treatment. Heart failure patients with relevant tricuspid annular dilatation undergoing TMVR for functional MR could therefore profit from a simultaneous tricuspid repair, even when TR has not yet reached advanced severity. Overall, there is an increasing amount of evidence supporting a more progressive treatment approach for secondary TR in which interventional TR treatment may represent a very promising complement in this area.

Patients with post-procedural TR improvement or TAD <34 mm revealed lower rates of post-procedural HHF with an association in the multivariable Cox regression analysis (TR improvement HR 0.6 [0.38-0.94] and TAD ≥34 mm HR 1.56 [1.06-2.29]). Although this might indicate a relevant role of TR improvement in clinical prognosis after TMVR, these findings must be interpreted with caution. Future studies are desirable to investigate whether TR development itself has an impact on prognosis, or if progressive functional TR is more an epiphenomenon of underlying heart failure deterioration leading to progressive TR. Nonetheless, our data indicate that TR development and heart failure are correlated, and that TR improvement and TAD decline can be considered as an additional marker of successful TMVR.

For surgical tricuspid therapy, tricuspid annulus, pulmonary hypertension, right ventricular dilation, and right ventricular dysfunction are parameters which have an influence on the decision making[1,18]. However, we did not find an association of echocardiographically estimated systolic pulmonary artery pressure with TR improvement, which is in contrast to prior studies[8,9]. Assessment of pulmonary artery pressure by echocardiography may have caused equalisation of right atrial and ventricular pressures in TR, and thus led to an underestimation[19]. Unfortunately, right heart catheterisation for higher accuracy of pulmonary pressure assessment was not performed routinely in the present study cohort. Here, patients with TR improvement had a smaller TAD, lower prevalence of AF and less residual MR at discharge. These parameters appeared very useful markers of TR reversibility after TMVR. Since less successful TMVR with post-procedural residual MR seems to be associated with worse outcome regarding TR development, surgical double valve treatment may be reconsidered, and may be a viable option in surgical candidates. Tricuspid annular dilatation is known to be associated with TR and poor prognosis[20]. In the present study, the best cut-off value was a TAD of ≥34 mm, and a decline of TAD indicated TR improvement. Moreover, patients with a remaining tricuspid annular dilatation at follow-up had a lower post-procedural event-free survival from HHF. Ultimately, TAD might serve as a sensitive marker for monitoring and decision making concerning concurrent mitral and tricuspid valve repair or TMVR-first followed by TTVR-second or no TTVR.

Study limitations

To the best of our knowledge, the present multicentre study included the largest patient cohort assessing this topic; however,

several limitations must be acknowledged. First, the study`s observational character warrants cautious interpretation and confirmation by controlled prospective studies. Second, there was no central echocardiography core laboratory and event adjudication. Furthermore, the number of follow-up echocardiographic assessments was limited. Analysis of post-procedural HHF must be interpreted with caution. The analysis of HHF rates and TR improvement/tricuspid annular dilatation showed a strong correlation; however, conclusions regarding pathophysiological causalities cannot be made. Finally, analysis of multiple variables is prone to confounders and the absence of statistical significance may be due to the sample size.

Conclusions

In patients undergoing TMVR, improvement of relevant TR (TR ≥II) is a frequent phenomenon within the first three months post TMVR. AF, rMR ≥II at discharge and TAD at baseline were independent and significant predictors preventing TR improvement and may help to define whether concomitant tricuspid valve disease should be treated immediately, second after a post-TMVR observational period, or not at all. Lastly, TR improvement and TAD <34 mm at follow-up were markers associated with lower rates of post-procedural heart failure hospitalisation.

Impact on daily practice

A MitraClip procedure for mitral regurgitation may lead to an improvement of relevant concomitant tricuspid regurgitation. Parameters which prevent this improvement are (1) atrial fibrillation, (2) post-procedural residual mitral regurgitation ≥II, and (3) tricuspid annular diameter (especially a tricuspid annular diameter of ≥34 mm). TAD represents a significant predictor which may be helpful in deciding between simultaneous mitral and tricuspid valve repair, or TMVR and re-evaluation of TR. The optimal timing of TR re-evaluation seemed to be at three months after a MitraClip procedure as improvement of TR was more likely to happen early after TMVR.

Conflict of interest statement

G. Nickenig has received speaker honoraria and research grants from Abbott, Abiomed, Medtronic, Boston Scientific, and Edwards Lifesciences, outside the submitted work. S. Baldus has received lecture honoraria from Edwards Lifesciences, Bayer Vital, CVRx, MSD Sharp & Dohme GmbH, JenaValve Technology, and Abbott, and research grants from Vifor Pharma, Symetis SA, Pfizer, JenaValve Technology, Valtech, OptumInsight, Biotronik and Abbott, outside the submitted work. R. Pfister has received speaker and consultant honoraria from Abbott and Edwards Lifesciences, outside the submitted work. C. Iliadis has received travel support from Abbott and speaker and consultant honoraria by Abbott and Edwards Lifesciences, outside the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Figure 1. Changes of tricuspid regurgitation over time.

Supplementary Table 1. Tricuspid regurgitation evolution according to availability of follow-up echocardiography.

Supplementary Table 2. Characteristics of patients with moderate or worse tricuspid regurgitation at baseline and improvement of tricuspid regurgitation at follow-up.

Supplementary Table 3. Analysis of heart failure medication at baseline versus at 3 months.

Supplementary Table 4. TR improvement and hospitalisation for heart failure.

Supplementary Table 5. Baseline characteristics according to tricuspid annular dilatation at follow-up.

Supplementary Table 6. Tricuspid annular dilatation and hospitalisation for heart failure.

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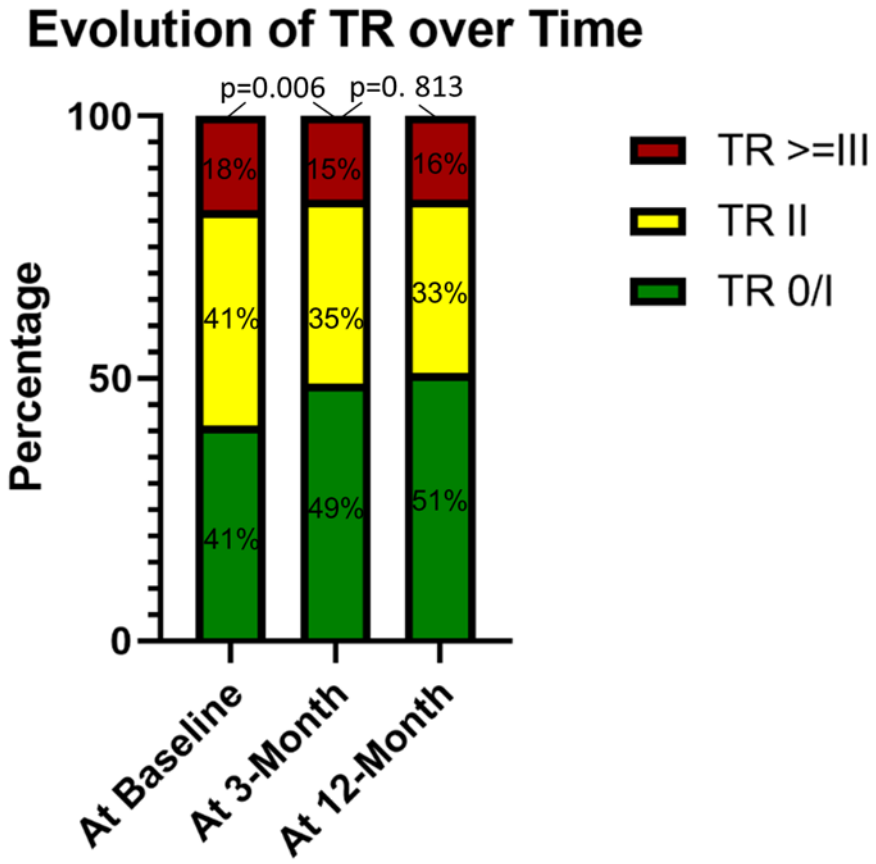
Supplementary data



Supplementary Figure 1. Changes of tricuspid regurgitation over time.

Comparing preprocedural and 3-month data, proportions of TR 0/I, II, and ≥III varied significantly (p=0.006), while the TR distributions changed only mildly comparing 3-month and 12-month data (p=0.813).

Supplementary Table 1. Tricuspid regurgitation evolution according to availability of follow-up echocardiography.

	Proportion of TR class at baseline			Proportion of TR class at 3 months			Proportion of TR class at 12 months		
	TR 0/I	TR II	TR ≥III	TR 0/I	TR II	TR ≥III	TR 0/I	TR II	TR ≥III
Total cohort (n=531)	41%	39%	19%	47% (+6%)	36% (-3%)	17% (-2%)	52% (+5%)	33% (-3%)	15% (-2%)
Subgroup									
With 3-month echocardiography available (n=485)	40%	41%	20%	47% (+7%)	36% (-5%)	17% (-3%)	51% (+4%)	33% (-3%)	16% (-1%)
With 12-month echocardiography available (n=392)	44%	39%	18%	49% (+5%)	35% (-4%)	15% (-3%)	52% (+3%)	33% (-2%)	15% (-0%)
With only 3-month echocardiography available (n=139)	35%	41%	24%	41% (+6%)	38% (-3%)	21% (-3%)			
With only 12-month echocardiography available (n=46)	61%	24%	15%				57% (-4%)	33% (+9%)	11% (-4%)

Numbers in brackets show the difference in TR development.

Supplementary Table 2. Characteristics of patients with moderate or worse tricuspid regurgitation at baseline and improvement of tricuspid regurgitation at follow-up.

	No TR improvement	TR improvement	*p*-value
Patients, n	184 (59%)	127 (41%)	
Clinical characteristics			
Age, years	79 (74-83)	78 (72-83)	0.925
Female gender	79 (43%)	53 (42%)	0.833
BMI, kg/m²	25.1 (22.9-28.7)	25.6 (22.7-28.5)	0.819
Diabetes	53 (29%)	36 (28%)	0.930
Prior stroke	33 (18%)	15 (12%)	0.142
COPD	35 (19%)	24 (19%)	0.978
Coronary artery disease	116 (63%)	80 (63%)	0.993
Atrial fibrillation	144 (78%)	76 (60%)	**<0.001**
Prior CABG	57 (31%)	35 (28%)	0.516
Prior valvular surgery	26 (14%)	10 (8%)	0.090
Pacemaker/ICD/CRT	76 (41%)	55 (43%)	0.725
Carotid stenosis	53 (29%)	35 (28%)	0.811
NYHA Class >II	162 (88%)	112 (88%)	0.969
Echocardiographic data			
Severe/massive TR	56 (30%)	46 (36%)	0.285
Residual MR at dc	71 (39%)	30 (24%)	**0.005**
Functional MR	115 (63%)	91 (72%)	**0.093**
LVEF, %	45 (33-58)	39 (28-55)	**0.032**
LVEDV	123 (89-171)	141 (97-193)	**0.086**
TAPSE	17 (15-22)	17 (14-20)	0.204
Systolic PAP, mmHg	50 (40-63)	51 (40-63)	0.606
Tricuspid annulus, mm	37 (33-43)	35 (31-40)	**0.013**
RV diameter	40 (30-48)	38 (29-46)	0.185
RA area, cm²	26 (21-32)	22 (19-31)	**0.084**
Laboratory assessment			
NT-proBNP, pg/mL	3,302 (1,776-6,461)	2,991 (1,868-6,385)	**<0.001**
GFR, ml/min	48 (36-64)	49 (37-64)	0.356
Haemoglobin, g/dl	11.8 (10.7-13.1)	12.2 (11.1-13.5)	**0.098**

Parameters with a p-value <0.100 were tested in the Cox regression analysis (bold).

Values are n (%), or median (interquartile range).

BMI: body mass index; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; dc: discharge; GFR: glomerular filtration rate; ICD: implantable cardioverter defibrillator; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association; PAP: pulmonary artery pressure; RA: right atrial; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation

Supplementary Table 3. Analysis of heart failure medication at baseline versus 3 months.

	Baseline vs 3 months				
	TR Class I (n=176)	TR Class II (n=179)	TR Class III (n=86)	TR improvement (n=108)	No TR improvement (n=157)
ACE inhibitor	48%/51% *p*=0.523	58%/55% *p*=0.359	45%/43% *p*=0.804	57%/55% *p*=0.508	51%/48% *p*=0.557
Ramipril, mg/d	5 (2.5-10)/5 (2.5-10) *p*=1.000 (n=65)	5 (2.5-6.9)/5 (2.5-5) *p*=0.996 (n=80)	5 (2.5-5)/5 (2.2-5) *p*=0.219 (n=26)	5 (2.5-5)/2.5 (2.5-5) *p*=0.855 (n=49)	5 (2.5-6.3)/5 (2.5-5) *p*=0.613 (n=57)
Enalapril, mg/d	20 (10-40)/20 (10-40) *p*=1.000 (n=7)	13 (4-20)/10 (4-20) *p*=1.000 (n=6)	n=2	10 (3-19)/13 (3-20) *p*=1.000 (n=4)	8 (3-18)/8 (3-10) *p*=1.000 (n=4)
Angiotensin receptor blocker	28%/30% *p*=0.607	23%/22% *p*=1.000	24%/21% *p*=0.508	23%/23% *p*=1.000	24%/21% *p*=0.454
Valsartan, mg/d	80 (80-160)/80 (60-160) *p*=0.500 (n=23)	80 (40-160)/160 (80-160) *p*=0.063 (n=15)	160 (40-160)/160 (16-160) *p*=0.750 (n=7)	80 (25-160)/160 (120-240) *p*=0.250 (n=9)	80 (60-160)/160 (70-160) *p*=0.438 (n=13)
Candesartan, mg/d	16 (8-16)/16 (6-16) *p*=0.875 (n=22)	8 (8-12)/8 (6-12) *p*=1.000 (n=9)	16 (8-32)/12 (5-22) *p*=0.250 (n=8)	8 (8-16)/8 (8-24) *p*=1.000 (n=7)	8 (4-20)/8 (4-16) *p*=0.250 (n=10)
Others, mg/d	50 (25-80)/45 (26-45) *p*=1.000 (n=16)	40 (25-48)/40 (40-95) *p*=0.250 (n=12)	n=1	40 (10-50)/40 (25-100) *p*=0.500 (n=7)	40 (35-50)/40 (35-140) *p*=1.000 (n=6)
Beta-blocker	88%/92% *p*=0.210	88%/92% *p*=0.210	85/87% *p*=0.754	88%/92% *p*=0.289	87%/89% *p*=0.481
Metoprolol, mg/d	95 (47.5-142)/95 (47.5-142) *p*=0.825 (n=50)	95 (47.5-142)/95 (47.5-111) *p*=0.197 (n=42)	95 (47.1-190)/95 (47.5-190) *p*=1.000 (n=18)	95 (47.5-190)/95 (47.5-142) *p*=0.359 (n=27)	95 (47.5-166)/95 (47.5-190) *p*=0.555 (n=33)
Bisoprolol, mg/d	5 (2.5-7.5)/5 (2.5-6.1) *p*=0.773 (n=77)	5 (2.5-7.5)/5 (2.5-7.5) *p*=0.548 (n=97)	5 (2.5-5)/5 (2.5-7.5) *p*=0.891 (n=43)	5 (2.5-8.8)/5 (2.5-7.5) *p*=0.952 (n=57)	5 (2.5-5.3)/5 (2.5-5.6) *p*=0.702 (n=74)
Others, mg/d	11 (5-25)/13 (5-25) *p*=0.848 (n=30)	13 (5-25)/13 (5-25) *p*=0.896 (n=23)	6 (4-13)/11 (5-22) *p*=0.313 (n=12)	13 (4-16)/13 (4-25) *p*=0.500 (n=10)	10 (5-25)/13 (5-25) *p*=0.924 (n=25)
MRA	35%/35% *p*=1.000	46%/45% *p*=0.845	47%/54% *p*=0.180	50%/54% *p*=0.388	44%/48% *p*=1.000

Spironolactone, mg/d	25 (25-25)/25 (25-25) *p*=0.891 (n=52)	25 (25-25)/25 (25-25) *p*=0.787 (n=61)	25 (25-50)/25 (25-38) *p*=0.844 (n=33)	25 (25-25)/25 (25-25) *p*=0.688 (n=45)	25 (25-25)/25 (25-25) *p*=0.941 (n=49)
Eplerenone, mg/d	25 (25-50)/25 (19-50) *p*=0.500 (n=5)	25 (25-50)/25 (25-50) *p*=0.500 (n=9)	n=3	25 (25-50)/25 (25-50) *p*=1.000 (n=5)	25 (13-50)/25 (25-50) *p*=0.500 (n=7)
Diuretics	85%/89% *p*=0.189	**91%/96%** ***p*=0.049**	91%/97% *p*=0.180	95%/98% *p*=0.453	**88%/95%** ***p*=0.019**
Torasemide, mg/d	11 (10-20)/15 (10-20) *p*=0.210 (n=118)	20 (10-30)/20 (10-30) *p*=0.580 (n=143)	20 (10-40)/20 (10-40) *p*=0.170 (n=71)	20 (10-40)/20 (10-30) *p*=0.086 (n=89)	20 (10-30)/20 (10-30) *p*=0.900 (n=125)
Furosemide, mg/d	40 (20-55)/40 (25-70) *p*=0.279 (n=17)	40 (20-80)/20 (20-80) *p*=0.203 (n=15)	60 (20-120)/30 (10-80) *p*=0.289 (n=11)	40 (20-85)/20 (20-60) *p*=0.071 (n=17)	60 (15-80)/40 (13-80) *p*=0.625 (n=9)
HCT, mg/d	13 (13-25)/13 (13-25) *p*=0.750 (n=25)	13 (13-25)/23 (13-25) *p*=0.211 (n=34)	19 (11-25)/25 (13-40) *p*=0.125 (n=8)	25 (13-25)/25 (13-25) *p*=0.125 (n=21)	25 (13-25)/25 (13-25) *p*=0.156 (n=21)
Xipamid, mg/d	10 (10-20)/10 (10-20) *p*=0.625 (n=11)	20 (10-25)/20 (10-25) *p*=0.797 (n=15)	11 (10-20)/20 (10-23) *p*=0.250 (n=14)	20 (10-20)/20 (20-20) *p*=0.500 (n=11)	10 (10-25)/16 (10-26) *p*=0.992 (n=11)
Digitalis glycosides	10%/13% *p*=0.146	17%/18% *p*=0.791	20%/21% *p*=1.000	19%/17% *p*=0.688	17%/20% *p*=0.302

Analysis of heart failure medication for patients with available 3-month data (n=441) showed that, comparing baseline and 3-month data, medication with ACE inhibitors (52% vs 51%; p=0.791), angiotensin receptor blockers (25% vs 25%; p=1.000), mineralocorticoid receptor antagonists (42% vs 43%; p=0.678) and digitalis glycosides (15% vs 17%; p=0.163) stayed similar, while beta-blockers (88% vs 91%; p=0.044) and diuretics (88% vs 93%; p=0.003) increased. Baseline and 3-month data regarding heart failure medication and daily doses were compared.

A p-value <0.05 was considered significant (bold).

HCT: hydrochlorothiazide; MRA: mineralocorticoid receptor antagonist

Supplementary Table 4. TR improvement and hospitalisation for heart failure.

	Cardiac hospitalisation			
	Univariable model		Multivariable model	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
TR improvement	0.65 (0.43-0.988)	**0.044**	0.6 (0.38-0.94)	**0.025**
Atrial fibrillation	1.1 (0.71-1.69)	0.666		
Functional MR	1,69 (1.07-2.68)	**0.024**	1.2 (0.69-2.11)	0.520
LVEF, per % increase	0.99 (0.98-1.002)	0.091	0.995 (0.38-1.01)	0.614
LVEDV, per ml increase	1.003 (1.001-1.006)	**0.016**	1.003 (0.999-1.006)	0.123
Tricuspid annulus, per mm increase	1.02 (1-1.05)	0.071	1.03 (0.997-1.06)	0.078
RA area, per cm^2 increase	0.99 (0.97-1.007)	0.199		
Residual MR ≥II at discharge	1.22 (0.9-1.68)	0.217		
NT-proBNP, per pg/mL increase	1 (1-1.00002)	0.319		
Haemoglobin, per g/dl increase	1.11 (0.97-1.25)	0.121		

A p-value <0.05 was considered significant (bold).

LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; RA: right atrial; TR: tricuspid regurgitation

Supplementary Table 5. Baseline characteristics according to tricuspid annular dilatation at follow-up.

	No tricuspid annular dilatation at follow-up	Tricuspid annular dilatation at follow-up	*p*-value
Patients, n	181 (40%)	273 (60%)	
Clinical characteristics			
Age, years	78 (73-82)	78 (73-82)	0.628
Female gender	97 (54%)	79 (29%)	**<0.001**
BMI, kg/m²	25.6 (23.0-29.7)	25.3 (22.9-28.4)	0.288
Diabetes	48 (27%)	78 (29%)	0.633
Prior stroke	19 (11%)	41 (15%)	0.164
COPD	34 (19%)	57 (21%)	0.585
CAD	141 (63%)	181 (67%)	0.436
Atrial fibrillation	102 (56%)	186 (68%)	**0.011**
Prior CABG	43 (24%)	92 (34%)	**0.023**
Prior valvular surgery	20 (11%)	31 (11%)	0.920
Pacemaker/ICD/CRT	54 (30%)	129 (47%)	**<0.001**
Carotid stenosis	36 (20%)	74 (27%)	**0.084**
NYHA Class >II	150 (83%)	229 (85%)	0.645
Echocardiographic data			
≥Severe TR	20 (11%)	66 (25%)	**<0.001**
Residual MR ≥II at dc	58 (32%)	88 (33%)	0.966
Functional MR	118 (65%)	184 (67%)	0.626
LVEF, %	44 (32-57)	42 (30-55)	0.118
LVEDV	126 (91-164)	150 (107-204)	**<0.001**
TAPSE	18 (16-22)	17 (15-21)	0.121
Systolic PAP, mmHg	47 (36-57)	48 (36-61)	0.297
RA area, cm²	20 (16-25)	26 (21-32)	**<0.001**
Laboratory assessment			
NT-proBNP, pg/mL	2,307 (1,001-4,964)	3,147 (1,611-6,441)	**0.001**
GFR, ml/min	49 (39-63)	49 (35-64)	0.816
Haemoglobin g/dl	12.3 (11.2-13.5)	12.0 (10.6-13.5)	**0.023**

Parameters with a p-value <0.100 were tested in the Cox regression analysis (bold).

Values are n (%), or median (interquartile range).

BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; dc: discharge; GFR: glomerular filtration rate; ICD: implantable cardioverter defibrillator; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association; PAP: pulmonary artery pressure; RA: right atrial; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation

Supplementary Table 6. Tricuspid annular dilatation and hospitalisation for heart failure.

	Univariable model		Multivariable model	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Tricuspid annular dilatation at FU	1.81 (1.26-2.60)	**0.001**	1.56 (1.06-2.29)	**0.023**
Female gender	0.78 (0.57-1.08)	0.136		
Atrial fibrillation	0.97 (0.71-1.34)	0.852		
Prior CABG	1.62 (1.18-2.22)	**0.003**	1.37 (0.96-1.93)	**0.080**
Pacemaker/ICD/CRT	1.53 (1.12-2.08)	**0.007**	1.27 (0.89-1.80)	0.185
Carotid stenosis	1.30 (0.93-1.83)	0.127		
Severe/massive TR	1.41 (0.98-2.04)	0.066		
LVEDV, per ml increase	1.003 (1.001-1.005)	**0.004**	1.002 (1-1.004)	0.174
RA area, per cm² increase	1.0 (0.998-1.02)	0.110		
NT-proBNP, per pg/mL increase	1 (1-1.00002)	0.111		
Haemoglobin, per g/dl increase	0.86 (0.79-0.94)	**<0.001**	0.86 (0.78-0.95)	**0.003**

A p-value <0.05 was considered significant (bold).

CABG: coronary artery bypass grafting; FU: follow-up; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; RA: right atrial; TR: tricuspid regurgitation