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RESEARCH ARTICLE

Characteristics and outcomes of patients with atrial versus ventricular secondary tricuspid regurgitation undergoing tricuspid transcatheter edge-to-edge repair – Results from the TriValve registry

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Aim

Functional or secondary tricuspid regurgitation (STR) is the most common phenotype of tricuspid regurgitation (TR) with atrial STR (ASTR) and ventricular STR (VSTR) being recently identified as two distinct entities. Data on tricuspid transcatheter edge-to-edge repair (T-TEER) in patients with STR according to phenotype (i.e. ASTR vs. VSTR) are lacking. The aim of this study was to assess characteristics and outcomes of patients with ASTR versus VSTR undergoing T-TEER.

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Methods and results Patients with STR undergoing T-TEER were selected from the Transcatheter Tricuspid Valve Therapies (TriValve) registry. ASTR was defined by (i) left ventricular ejection fraction ≥50%, (ii) atrial fibrillation, and (iii) systolic pulmonary artery pressure <50 mmHg. Patients not matching these criteria were classified as VSTR. Patients with primary TR and cardiac implantable electronic device were excluded. Key endpoints included procedural success and survival at follow-up. A total of 298 patients were enrolled in the study: 65 (22%) with ASTR and 233 (78%) with VSTR. Procedural success was similar in the two groups (80% vs. 83% for ASTR vs. VSTR, $p = 0.56$) and TEER was effective in reducing TR in both groups (from 97% of patients with baseline TR ≥3+ to 23% in ASTR and to 15% in VSTR, all $p = 0.001$). At 12-month follow-up, survival was significantly higher in the ASTR versus VSTR cohort (91% vs. 72%, log-rank $p = 0.02$), with VSTR being an independent predictor of mortality at multivariable analysis (hazard ratio 4.75).

Conclusions In a real-world, multicentre registry, T-TEER was effective in reducing TR grade in both ASTR and VSTR. At 12-month follow-up, ASTR showed better survival than VSTR.

Keywords Transcatheter tricuspid valve interventions • Transcatheter edge-to-edge repair • Atrial secondary tricuspid regurgitation • Ventricular secondary tricuspid regurgitation

Introduction

Functional or secondary tricuspid regurgitation (STR) represents the most common aetiology (~90%) of tricuspid regurgitation (TR).[1] Several studies demonstrated that, if left untreated, STR has a negative impact on long-term outcomes and the patient's quality of life.[2–7] Since it represents the most common underlying cause of TR, burdened by high mortality, a deep understanding of this condition is of utmost importance.[8]

While STR has been traditionally attributed to pulmonary hypertension or left heart disease which results in right ventricular (RV) dysfunction and/or dilatation, more recently, the entity once referred to as 'idiopathic' TR, has now been recognized as a distinct entity with different right heart and tricuspid valve morphology characterized by marked annular and right atrial (RA) dilatation (atrial STR [ASTR]).[9] This entity has distinct aetiology and different natural history from ventricular/non-atrial STR (VSTR).[10,11] ASTR is frequently associated with atrial fibrillation (AF) and is the result of the increase in annular area that accompanies RA enlargement.[12] Instead, VSTR is characterized by leaflet tethering caused by papillary muscle displacement following RV remodelling. Currently, ASTR definition is not univocal although the absence of RV systolic dysfunction and normal pulmonary artery pressure are common features across all the definitions.[13–15]

A few data exist on clinical outcomes of patients with STR conservatively managed and according to STR phenotype (i.e. ASTR vs. VSTR).[11,16,17] Moreover, the role of STR phenotype in patients undergoing tricuspid transcatheter edge-to-edge repair (T-TEER) is unknown. Thus, the aim of the present study is to investigate clinical and echocardiographic characteristics, and procedural and clinical outcomes of patients with ASTR versus VSTR receiving T-TEER.

Methods

Study population and definitions

The Transcatheter Tricuspid Valve Therapies (TriValve) international registry is a multicentre registry collecting patient-level data with symptomatic, at least severe TR undergoing transcatheter tricuspid valve intervention (TTVI) with multiple devices. In this study, only patients undergoing T-TEER from 2015 to 2022 were selected (*Figure 1*). In particular MitraClip (Abbott Vascular, Abbott Park, IL, USA), TriClip (Abbott Vascular) and PASCAL (Edwards Lifesciences, Irvine, CA, USA) were used for T-TEER.

All patients enrolled in the registry were discussed in the local multidisciplinary Heart Team. Clinical and echocardiographic data were

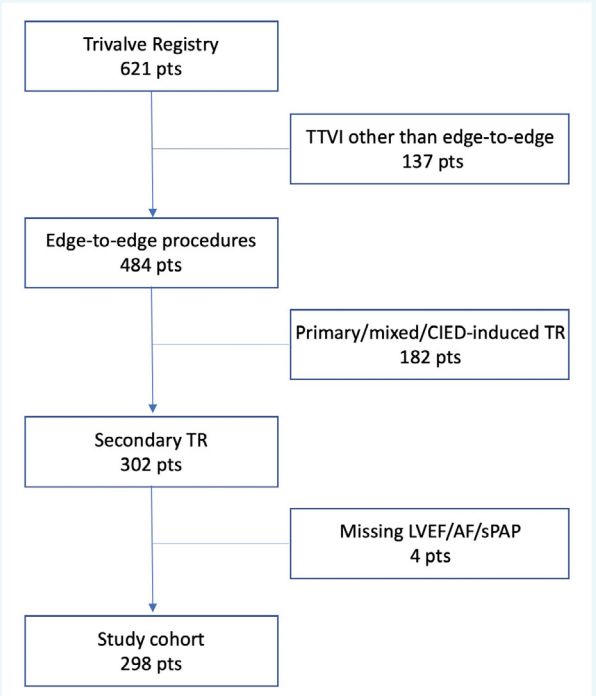


Figure 1 Flow-chart for study population selection. AF, atrial fibrillation; CIED, cardiac implantable electronic device; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; TTVI, transcatheter tricuspid valve intervention.

collected at baseline. Grading of TR severity was based on the integration of semi-quantitative and quantitative measures, as described by the American Society of Echocardiography guidelines as well as the European Association of Cardiovascular Imaging guidelines.[18,19] Tricuspid annulus (TA) diameter was obtained at end-diastole from the echocardiographic standard apical four-chamber view. Echocardiographic measurements were self-reported by each centre and were performed within 72 h before and after the TEER procedure. Follow-up events and echocardiographic findings were collected whenever available from the respective centres.

Atrial STR was defined if patients met all the following criteria: (i) left ventricular ejection fraction (LVEF) >50% without wall motion abnormalities; (ii) AF; and (iii) estimated systolic pulmonary artery pressure (sPAP) <50 mmHg. Patients with primary TR and/or with cardiac implantable electronic device (CIED) were excluded from this study.

Procedural success was defined by the combination of successful device implantation and TR reduction to ≤2+. High-dose diuretics were defined as administration of furosemide >125 mg/die. Elevated bilirubin was defined as a value above the laboratory threshold while N-terminal pro-B-type natriuretic peptide (NT-proBNP) was defined elevated when >220 pg/ml (sinus rhythm) or >660 pg/ml (AF).[20–22]

All necessary ethical oversight was secured. The study is in line with the Declaration of Helsinki, and the local ethic committees approved the investigation. The TriValve registry is registered at ClinicalTrials.gov (NCT03416166).

Table 1 Baseline clinical and echocardiographic characteristics of the study groups

	ASTR (*n* = 65)	VSTR (*n* = 233)	*p*-value
Age, years	77 ± 8	77 ± 9	0.91
Male sex, *n* (%)	21 (32)	107 (46)	0.036
STS score	4.2 ± 2.9	5.7 ± 5.1	0.06
TRI-SCORE	3.9 ± 1.7	4.2 ± 1.9	0.24
Medical history, *n* (%)			
AF baseline	65 (100)	127 (55)	<0.001
Diabetes	23 (35)	57 (24)	0.08
Haemodynamic instability	0 (0)	9 (4)	0.21
Prior CAD	15 (23)	74 (32)	0.22
COPD	13 (17)	41 (18)	0.71
NYHA class III/IV	56 (86)	214 (92)	0.32
Prior admission for RV failure	34 (52)	170 (72)	0.001
High-dose diuretics	15 (23)	71 (30)	0.35
Laboratory exams			
Anaemia, *n* (%)	48 (73)	155 (66)	0.22
eGFR, ml/min/1.73 m^2	48 ± 18	47 ± 20	0.61
eGFR <60 ml/min/1.73 m^2, *n* (%)	49 (77)	170 (74)	0.63
Elevated bilirubin, *n* (%)	30 (46)	98 (42)	0.92
Elevated NT-proBNP, *n* (%)	36 (55)	162 (70)	0.03
Echocardiography			
LVEF, %	59 ± 6	49 ± 13	<0.001
LVEF ≥50%, *n* (%)	65 (100)	129 (55)	<0.001
LVEF 41–49%, *n* (%)	/	44 (19)	
LVEF ≤40%, *n* (%)	/	60 (26)	
LVEDD, mm	47 ± 7	50 ± 8	0.005
LA Vol, ml/m^2	51 ± 24	59 ± 32	0.08
RA Vol, ml/m^2	68 ± 40	54 ± 32	0.015
TAPSE, mm	18 ± 6	17 ± 5	0.18
EROA, cm^2	0.7 ± 0.7	0.6 ± 0.4	0.13
Annular diameter, mm	47 ± 7	47 ± 7	0.84
sPAP >50 mmHg, *n* (%)	0 (0)	81 (35)	<0.001
MR >2 baseline, *n* (%)	10 (15)	101 (43)	<0.001
TR <3+ post-procedure, *n* (%)	50 (77)	188 (81)	0.28

AF, atrial fibrillation; ASTR, atrial secondary tricuspid regurgitation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; LA, left atrium; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure; RA, right atrium; RV, right ventricle; STS, Society of Thoracic Surgeons; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; Vol, volume; VSTR, ventricular secondary tricuspid regurgitation.

Statistical analysis

Continuous variables are presented as means with standard deviation (SD) or medians with interquartile range (25th–75th, IQR), according to variable distribution. Categorical variables are presented as numbers and percentages of total. The Shapiro–Wilk test was used to test the normality of the distributions. Continuous variables were evaluated using a parametric test (Student's *t*-test) or a non-parametric test (Mann–Whitney test), as appropriate. Categorical variables were evaluated using χ^2 test or Fisher's exact test, as appropriate.

The survival was defined as the time from the date of T-TEER until death due to any cause. Patients not known to have died at the time of analysis were censored based on the last recorded date on which they were known to be alive. The Kaplan–Meier method was used to plot the unadjusted overall 1-year survival curves. Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the overall survival. Crude and adjusted analyses were conducted. In the latter, we adjusted for the covariates that emerged as differently distributed in the univariate analysis at a *p*-value <0.005. A total of six baseline variables arranged in a dichotomous fashion were entered in the conventional multivariate model by univariate preselection. Schoenfeld residuals were used to formally test the Cox proportional hazards assumption for each covariate. All variables included in the analysis were complete or had less than 15% of missing data.

A 2-tailed, *p*-value <0.05 was established as the level of statistical significance. All statistical analyses were performed using SPSS software version 25.0 (IBM Corporation, Armonk, NY, USA).

Table 2 Procedural data

	ASTR (*n* = 65)	VSTR (*n* = 233)	*p*-value
Procedural time, min	118 ± 52	129 ± 58	0.20
Length of stay, days	3 ± 3	4 ± 5	0.10
Device type, *n* (%)			
MitraClip	59 (91)	228 (98)	0.06
TriClip/PASCAL	6 (9)	5 (2)	
Clips implanted, *n* (%)			
1	13 (20)	53 (23)	0.85
2	33 (51)	116 (50)	
≥3	19 (29)	64 (27)	
Procedural success, *n* (%)	52 (80)	193 (83)	0.56
Concomitant MV interventions, *n* (%)	14 (21)	65 (36)	0.05
Complications			
Device delivery failure, *n* (%)	3 (5)	3 (1)	0.11
Conversion to surgery	1	1	0.46
Stroke	3	1	0.07
MI	0	0	/
Infections	4	6	0.48

ASTR, atrial secondary tricuspid regurgitation; MI, myocardial infarction; MV, mitral valve; VSTR, ventricular secondary tricuspid regurgitation.
Procedural success: device successfully implanted with tricuspid regurgitation reduction to ≤2+.

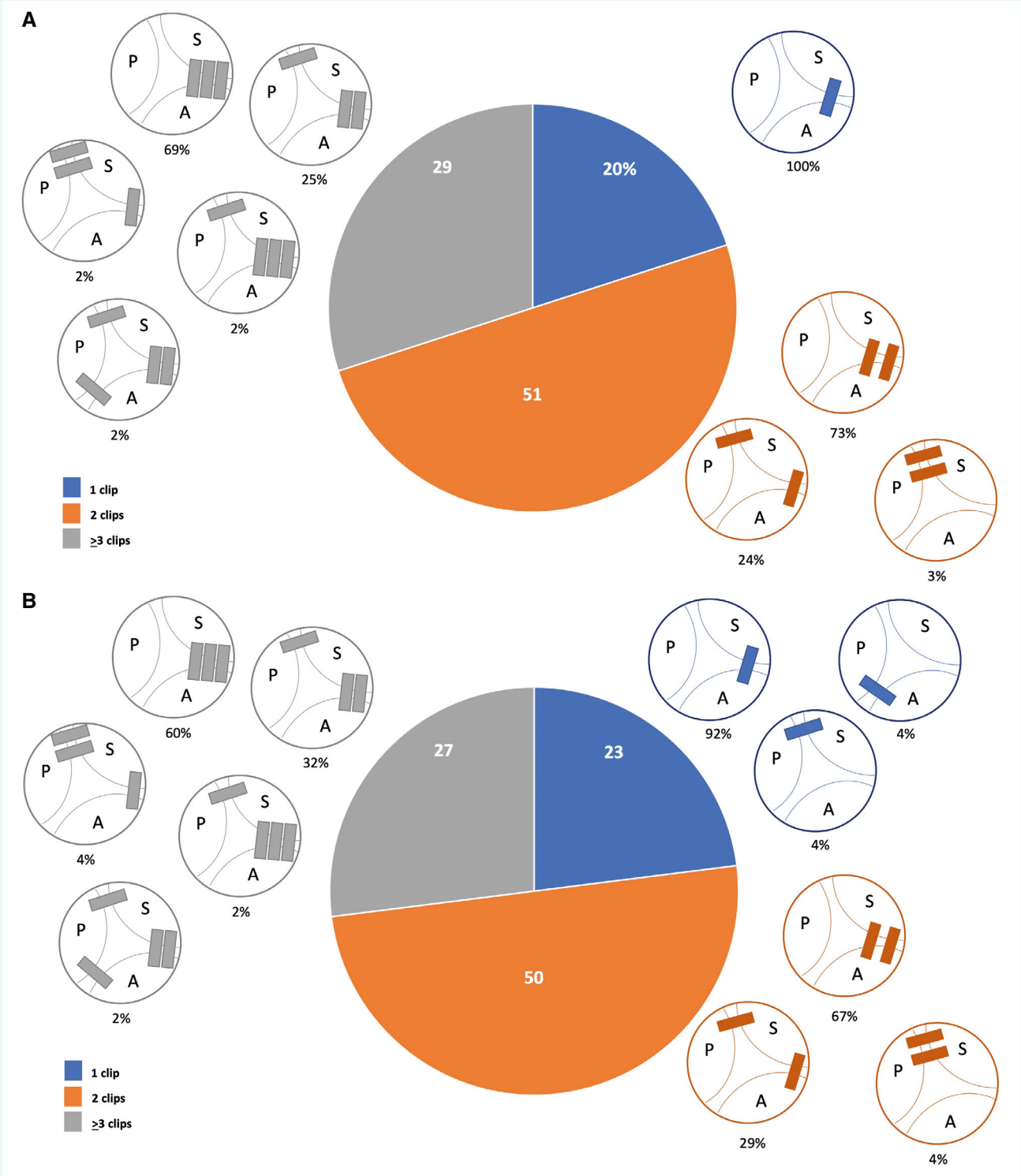


Figure 2 Anatomical distribution of implanted clips in the atrial secondary tricuspid regurgitation (*A*) and ventricular secondary tricuspid regurgitation (*B*) groups. A, anterior leaflet; P, posterior leaflet; S, septal leaflet.

Results

Clinical and echocardiographic data

Among the 298 patients included, 65 (22%) had ASTR and 233 (78%) had VSTR. Baseline demographic, clinical and echocardiographic characteristics are summarized in *Table 1*. Male patients were more frequent in the VSTR group as compared to the ASTR group (46% vs. 32%, $p = 0.036$). Prior hospitalizations for RV failure were significantly more common in VSTR as compared to ASTR (72% vs. 52%, $p = 0.001$). Of note, among patients with VSTR, 55% had LVEF ≥50%, 55% showed AF and 51% and sPAP <50 mmHg. Finally, VSTR patients were more likely to have a history of prior coronary artery disease (CAD), chronic obstructive pulmonary disease and New York Heart Association functional class III/IV (p = NS). No significant differences were observed for laboratory exams except for NT-proBNP which was more frequently elevated in VSTR patients (median [IQR]: 2157 [2068] pg/ml vs. 2874 [4089] pg/ml, $p = 0.007$ for ASTR vs. VSTR).

With regard to echocardiography data, patients with VSTR showed lower values of LVEF (mean ± SD: 49 ± 13% vs. 59 ± 6%, $p < 0.001$) and larger LV end-diastolic diameter (mean ± SD: 50 ± 8 vs. 47 ± 7 mm, $p = 0.005$) as compared to those with ASTR. As expected, indexed RA volume was larger in the ASTR cohort as compared to VSTR group (mean ± SD: 68 ± 40 vs. 54 ± 32 ml/m^2, $p = 0.015$). As by definition, no patients of the ASTR group had sPAP >50 mmHg whereas it was observed in 35% of patients with VSTR. Significant mitral regurgitation (MR) at baseline was significantly more frequent in VSTR versus ASTR (43% vs. 15%,

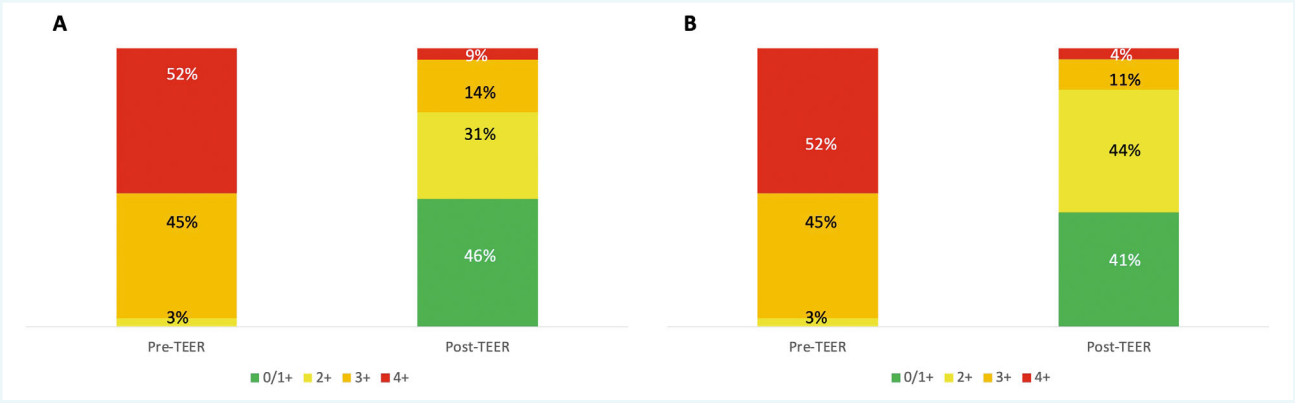
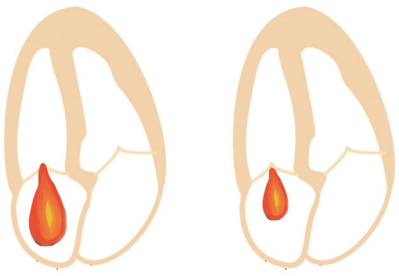


Figure 3 Pre- and post-transcatheter edge-to-edge repair (TEER) tricuspid regurgitation grades in the atrial secondary tricuspid regurgitation (*A*) and ventricular secondary tricuspid regurgitation (*B*) groups.



	Pre-TTVI	Post-TTVI	p
ASTR			
Regurgitant Volume, *ml/beat*	46± 22	22± 13	<0.001
EROA, *mm²*	51± 28	22± 14	<0.001
VSTR			
Regurgitant Volume, *ml/beat*	48± 27	28± 23	<0.001
EROA, *mm²*	55± 33	28± 25	<0.001

Figure 4 Tricuspid regurgitation grade as defined by regurgitant volume and effective regurgitant orifice area (EROA) before and after intervention. ASTR, atrial secondary tricuspid regurgitation; TTVI, transcatheter tricuspid valve intervention; VSTR, ventricular secondary tricuspid regurgitation.

$p < 0.001$). No significant differences were reported for left atrial volume, RV function, effective regurgitant orifice area, annular diameter and residual TR.

Procedural data

Procedural data are shown in *Table 2*. T-TEER was mostly performed with MitraClip device and only in few cases with TriClip or PASCAL. Number of implanted clips and clip distribution is summarized in *Table 2* and *Figure 2*.

Procedural success was achieved in 80% of patients with ASTR versus 83% of patients with VSTR ($p = 0.56$). In six cases (three ASTR and three VSTR), procedural failure was due to unsuccessful clip implantation. Concomitant mitral valve interventions were more common among VSTR patients than ASTR patients (36% vs. 21%, $p = 0.05$).

Degree of TR was significantly reduced after TEER in both groups ($p < 0.001$) (*Figures 3* and *4*). In particular, post-procedural TR ≤2+ was achieved in 77% of patients with ASTR and in 85% with VSTR.

Clinical outcomes

Atrial STR was associated with better survival as compared to VSTR (91% vs. 72%, log-rank $p = 0.02$) at a median follow-up time of 10 months (IQR 5–13 months) (*Figure 5*).

According to multivariate analysis, acute procedural success was an independent protective factor for mortality risk (HR 0.41, 95% CI 0.17–0.96, $p = 0.041$). VSTR and the use of high-dose diuretics were almost significant (HR 2.94, 95% CI 0.97–8.94, $p = 0.057$; and HR 2.11, 95% CI 0.99–4.47, $p = 0.051$, respectively) (*Table 3*). The three variables defining ASTR were also analysed separately from each other and no significant differences in survival were found between ASTR and VSTR groups (*Figure 6*).

Discussion

The main findings of this study are (i) in patients with STR undergoing T-TEER, ASTR has a prevalence of 22%; (ii) patients with ASTR have different clinical and echocardiographic characteristics as compared to those with VSTR; and (iii) ASTR is independently associated with a better survival than VSTR, despite similar procedural success.

So far, atrial dysfunction has been considered a marker or consequence of other cardiac conditions rather than an independent clinical entity and the concept of 'atrial failure' or 'atrial disease' has been introduced only recently.[23,24] Recent data have shown that permanent AF is associated with increased risk of developing TR and that significant TR impacts negatively on survival.[25] Therefore, ASTR can be considered as a relatively 'new' clinical entity with multiple definitions being recently proposed. In a recent European expert position paper by the PCR Tricuspid Focus Group, a new integrated classification of TR has been proposed with ASTR reported as a specific subgroup of STR and defined with the presence of RA enlargement and dysfunction leading to significant isolated annular dilatation and often normal right ventricle.[9] Current European guidelines do not distinguish between atrial and

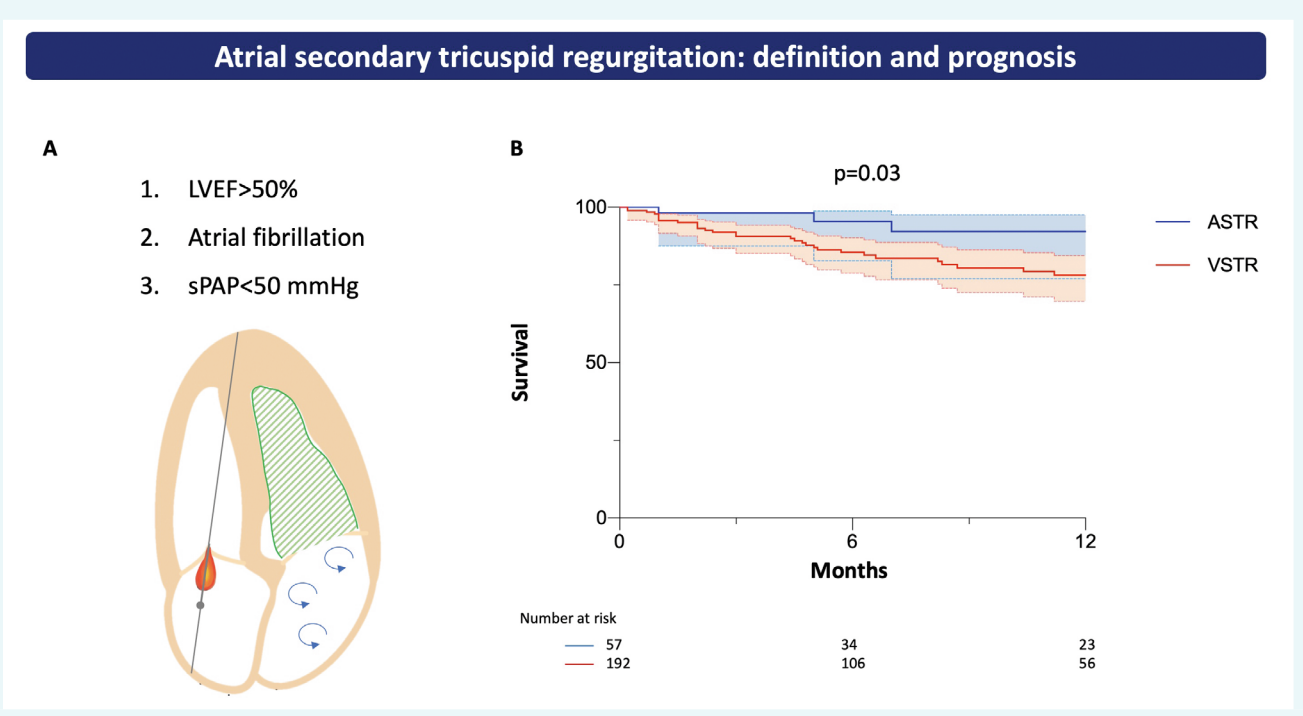


Figure 5 Definition of atrial secondary tricuspid regurgitation (ASTR) (A) and survival Kaplan–Meier curves for ASTR and ventricular STR (VSTR) groups (B). LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure.

Table 3 Univariate and multivariate analysis for mortality risk prediction

	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Group VSTR	4.75	1.12–20.18	0.03	2.94	0.97–8.94	**0.057**
Age ≥75 years	1.40	0.66–2.97	0.38	1.66	0.67–4.12	0.27
Male sex	1.38	0.72–2.63	0.32	–	–	–
BMI ≥25 kg/m^2	0.55	0.26–1.16	0.12	–	–	–
Elevated bilirubin	3.41	0.40–28.79	0.26	–	–	–
Elevated NT-proBNP	2.23	0.96–5.18	0.06	1.14	0.42–3.09	0.78
GFR <60 ml/min	1.91	0.80–4.59	0.15	–	–	–
MR >2+ baseline	1.52	0.79–2.92	0.21	–	–	–
TAPSE <17 mm	2.35	1.13–4.85	0.021	1.89	0.86–4.16	0.11
High-dose diuretics	2.67	1.33–5.35	0.004	2.11	0.99–4.47	**0.051**
Acute procedural success	0.20	0.10–0.39	<0.001	0.41	0.17–0.96	**0.041**

AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VSTR, ventricular secondary tricuspid regurgitation.

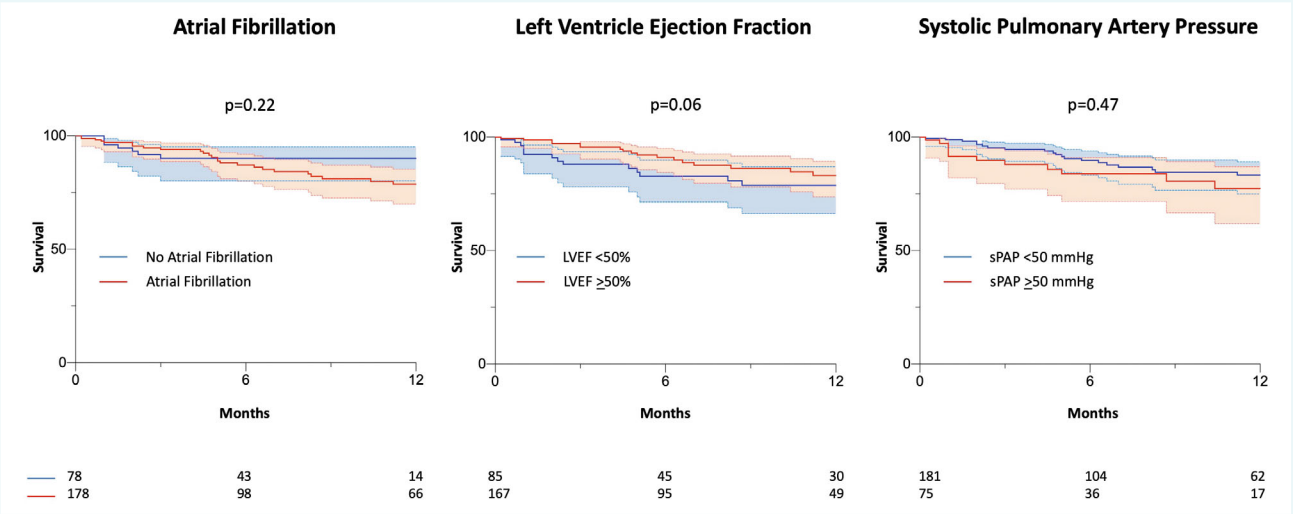


Figure 6 Kaplan–Meier survival curves for patients with and without atrial fibrillation, with left ventricular ejection fraction (LVEF) ≥50% or <50% and with systolic pulmonary artery pressure (sPAP) ≥50 or <50 mmHg.

ventricular/non-atrial secondary valve regurgitations,[26] while those from the American Heart Association/American College of Cardiology use the following criteria to define isolated TR (i.e. ASTR)[27]: (i) AF, (ii) LVEF >60%, (iii) sPAP <50 mmHg, (iv) no left-sided valve disease, and (v) normal-appearing tricuspid valve leaflets. Schlotter *et al.*[16] identified other morphologic characteristics of ASTR: (i) tenting height ≤10 mm, (ii) RV midventricular diameter ≤38 mm, and (iii) LVEF ≥50%. Of note, this definition was based on a cluster analysis although it did not include parameters related with RA function (RA dilatation or AF) nor sPAP. Galloo *et al.*[28] identified ASTR by exclusion, namely as absence of RV dysfunction, pulmonary hypertension and left-sided valve disease. Populations included in these two studies had similar baseline clinical characteristics: greater female prevalence, lower NT-proBNP and higher LVEF. In addition, both studies suggest that ASTR makes up around 20% of patients with STR conservatively managed. Our results are in line with those reported above in terms of both ASTR prevalence and patient characteristics. Compared with previous definitions, ours is based on clinical parameters that can be easily identified in large databases. However, the prevalence of ASTR may be underestimated in our and previous studies because of the exclusion of patients with CIED. ASTR patients may, however, represent a specific subgroup and the separate analysis of the three variables defining ASTR (*Figure 6*) suggest the importance of identifying such subgroup as for none of the three variables alone were observed differences in survival.

Notably, the patient included in our study underwent TR correction by means of T-TEER. Thus, to the best of our knowledge this

is the first study comparing ASTR and VSTR in patients undergoing T-TEER. We found a similar procedural success in ASTR versus VSTR patients: this would imply that any potential anatomical difference between two TR mechanisms (leaflet coaptation, tenting height and leaflet tension) do not affect acute procedural outcomes. Importantly, despite comparable procedural success, survival at 12 months differed significantly with ASTR showing higher survival than in the VSTR group. Of note, acute procedural success was a protective factor in relation to mortality risk at multivariate analysis.

Taking together the recent data on secondary MR, this study confirms that atrial and ventricular functional regurgitation are different clinical entities and are associated with different prognosis with atrial showing better survival than ventricular/non-atrial aetiology.[15,16,29] These results would suggest that ventricular component of functional heart valve disease has a worse impact on patient survival than the atrial mechanism, although some overlap between the two conditions might exist, as shown in the present population. Indeed, it is well known that heart failure with preserved ejection fraction, a clinical condition often associated with atrial remodelling, AF and atrioventricular valve insufficiency, is associated with a better prognosis as compared to heart failure with reduced ejection fraction.[30,31] Patients with VSTR had, on the other hand, a very poor outcome with 12-month survival of only 72%.

Notably, the recent TRILUMINATE Pivotal trial showed benefit of T-TEER compared to conservative care in TR patients, mainly driven by a significant improvement in quality of life and with a concomitant low rate of mortality and heart failure hospitalization in both arms.[32] The low rate of events observed in the study can be related to the characteristics of the included TR population, which are very close to a ASTR phenotype. Indeed, most patients had preserved ejection fraction and AF. Taking together these data and our findings, we may speculate that patients with ASTR are the best candidates for transcatheter TR treatment since we may expect a high procedural success and a good prognosis. On the other hand, in patients with VSTR a better selection aiming at identifying an earlier stage of ventricular disease may probably be more appropriate. However, although the great effort to identify possible predictors of favourable outcomes after TTVI, further research is needed to clarify whether some patient profile (i.e. ASTR vs. VSTR) may have an impact on the treatment effect of T-TEER on long-term outcomes.[33,34]

Limitations

The present study has some limitations. First, this is multicentre registry without an echocardiographic core lab. Second, different T-TEER devices were used in this investigation although 95% of cases were performed with the same one (MitraClip). Third, while a universal ASTR definition is lacking thus far and imperfections may remain, the ASTR definition was based on previous definitions of ASTR and on recent definition of atrial secondary MR. Fourth, as a retrospective study based on a multicentre registry, there are some missing data which could not be included in the analysis but would have been interesting information (e.g. heart failure medication, echocardiographic strain analysis, post-procedural rhythm, etc.). Finally, no propensity score matching was performed, although all patients enrolled belong to the same registry.

Conclusions

Atrial STR, defined as LVEF ≥50%, AF and sPAP <50 mmHg, has a prevalence of 22%, with different clinical and echocardiographic characteristic from VSTR. Despite similar procedural success, ASTR is associated with a significantly better survival than VSTR.

Conflict of interest: none declared.

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