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FOCUS ON TRICUSPID VALVE REPAIR

ORIGINAL RESEARCH: STRUCTURAL

Atrial Secondary Tricuspid Regurgitation

Insights Into the EuroTR Registry

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ABSTRACT

BACKGROUND Atrial secondary tricuspid regurgitation (A-STR) has been proposed as an important etiologic subentity of secondary tricuspid regurgitation (STR). Patients with A-STR are frequently treated using transcatheter tricuspid valve edge-to-edge repair (T-TEER).

OBJECTIVES The aims of this study were to evaluate prevalence and outcomes following T-TEER for severe A-STR and to compare the results to patients with nonatrial STR.

METHODS The study included patients from the EuroTR (European Registry of Transcatheter Repair for Tricuspid Regurgitation) registry who underwent T-TEER for STR from 2016 until 2022. A-STR was defined as a ratio of end-systolic right atrial area to right ventricular area ≥1.5 in the presence of preserved right ventricular function (tricuspid annular plane systolic excursion >17 mm). The primary study endpoint was 2-year survival free from heart failure hospitalization. Secondary endpoints were 2-year survival, tricuspid regurgitation (TR) reduction at discharge and 1-year follow-up as well as changes in NYHA functional class.

RESULTS This study included 641 patients (50% women) with a mean age of 79 ± 7 years. The overall prevalence of A-STR was 31% (n = 196). A-STR was associated with a higher prevalence of atrial fibrillation, less frequent comorbidities, better biventricular function, less leaflet tenting, and larger atria. Although TR severity was comparable at baseline, patients with A-STR had more effective procedural TR reduction (TR ≤2+ in 86.9% vs 80.4% of those with nonatrial STR; $P = 0.005$). Although NYHA functional class improved in both STR subetiologies, the symptomatic burden was lower in patients with A-STR at the latest available follow-up (NYHA functional class ≥III in 46% of patients with nonatrial STR vs 38% in those with A-STR; $P = 0.033$). Beyond that, A-STR was associated with higher 2-year survival rates free from heart failure hospitalization (66.3% [Q1-Q3: 58.2%-75.5%] vs 47.5% [Q1-Q3: 41.7%-54.7%] in patients with nonatrial STR; $P < 0.001$). Median survival follow-up was 379 days [Q1-Q3: 155-697 days].

CONCLUSIONS A-STR is a common phenotype of STR and is associated with effective TR reduction and symptomatic reduction after T-TEER. (JACC Cardiovasc Interv. 2024;17:2781-2791) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

A-STR = atrial secondary tricuspid regurgitation

CIED = cardiac implantable electronic device

HHF = heart failure hospitalization

LVEF = left ventricular ejection fraction

RA = right atrial/atrium

RV = right ventricle/ventricular

STR = secondary tricuspid regurgitation

TAPSE = tricuspid annular plane systolic excursion

TR = tricuspid regurgitation

T-TEER = transcatheter tricuspid valve edge-to-edge repair

TVARC = Tricuspid Valve Academic Research Consortium

Tricuspid regurgitation (TR) is associated with substantial morbidity, mortality, and reduced quality of life.[1] Transcatheter tricuspid valve edge-to-edge repair (T-TEER) has emerged as a safe, minimally invasive, and effective treatment approach for patients with severe TR.[2-6] The first randomized controlled trial in interventional TR treatment (TRILUMINATE) demonstrated T-TEER to be superior to diuretic treatment alone in enhancing quality of life, as evaluated using the Kansas City Cardiomyopathy Questionnaire.[7] Despite the absence of significant differences in heart failure hospitalization (HHF) and survival, patient selection remains a subject of intense debate.[8]

TR is an extremely heterogeneous disease entity concerning clinical presentation, treatment response, and etiology.[9] With respect to recent guidelines, TR is classified into primary, secondary, and cardiac implantable electronic device (CIED)-related TR.[10,11] Most patients being treated with T-TEER exhibit secondary TR (STR) or CIED-related TR. As on the mitral side,[12,13] it has been proposed to subdivide STR into atrial STR (A-STR) and ventricular STR phenotypes. A-STR occurs in patients with long-standing (permanent or persistent) atrial fibrillation (AF) and/or restrictive hemodynamic status, as in heart failure with preserved ejection fraction. The recently published Tricuspid Valve Academic Research Consortium (TVARC) consensus paper proposes several echocardiographic criteria for the identification of patients with A-STR.[14] A pivotal characteristic of A-STR is the disproportionate enlargement of the right atrium (RA) relative to the right ventricle (RV), coupled with preserved RV function.[15] In this study, we categorized real-world T-TEER patients from a large international registry into STR subtypes (atrial vs nonatrial) according to a pathophysiology-based approach based on the TVARC consensus document[14] and a recent state-of-the-art paper[15] and assessed the impact of A-STR on survival and symptomatic outcomes.

METHODS

STUDY COHORT, VARIABLES, AND ENDPOINTS. The study used data from the EuroTR (European Registry of Transcatheter Repair for Tricuspid Regurgitation) registry, which included patients with TR who underwent T-TEER from 2016 until 2022 at 20 European study sites (NCT06307262). The inclusion criteria were limited to patients with STR and available information on tricuspid annular plane systolic excursion (TAPSE) and end-systolic RA or RV area. Concomitant transcatheter mitral valve edge-to-edge repair led to exclusion from this study (Supplemental Figure 1). Patient selection involved interdisciplinary consensus within local heart teams, considering factors such as comorbidities, symptoms, anatomy, and life expectancy, under maximum

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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tolerated medical treatment. The T-TEER procedure was performed using either the PASCAL device (Edwards Lifesciences) or the MitraClip/TriClip system (Abbott Vascular), as previously described.[16] The study conforms with the principles outlined in the Declaration of Helsinki and was approved by each center's local ethics committee.

Echocardiographic analyses were performed by experienced physicians at each center according to recent recommendations.[17,18] Echocardiographic evaluation included tenting height, tenting area, RV midventricular diameter, RV end-systolic area, RA end-systolic area, TAPSE, RV fractional area change, and left ventricular ejection fraction (LVEF). In line with recent recommendations, A-STR was defined as a ratio of RA end-systolic area to RV end-systolic area ≥1.5 in the presence of preserved RV function (TAPSE >17 mm).[14,15] The primary study endpoint was 2-year survival free from HHF. Secondary outcomes included change in NYHA functional class and change in TR severity from baseline to latest available follow-up.

STATISTICAL ANALYSIS. Data are expressed as mean ± SD or median (Q1-Q3), as appropriate. Two-year survival rates were depicted using Kaplan-Meier charts. Statistical significance of survival differences was assessed using the log-rank test. The proportional hazards assumption was tested using the Cox proportional hazards regression test with time-dependent covariates. Parameters with P values <0.05 in a univariable Cox regression analysis were included in a multivariable backward elimination model. Differences between 2 independent samples were evaluated using the Mann-Whitney U test. Dependent samples were compared by applying the Wilcoxon test. A 2-sided P value of <0.05 was considered to indicate statistical significance. All analyses were performed using R version 4.0.4 (R Foundation for Statistical Computing) and SPSS version 25 (IBM).

RESULTS

BASELINE CHARACTERISTICS AND STUDY OUTCOMES. The study included 641 patients (50% women) with increased surgical risk (European System for Cardiac Operative Risk Evaluation II score 4.7% [Q1-Q3: 2.6%-7.5%], TRI-SCORE 7 points [Q1-Q3: 5-8 points]) at a mean age of 79.0 ± 7.1 years. TR severity was torrential (5+) in 18.7%, massive (4+) in 30.4%, severe (3+) in 47.7%, and moderate (2+) in 23.2% of patients. Mean TR effective regurgitant orifice area and regurgitant volumes were 0.54 cm^2 [Q1-Q3: 0.40-0.76 cm^2] and 64.0 mL [Q1-Q3: 34.0-61.0 mL], respectively. End-systolic dimensions of the RA and RV were 36.9 ± 12.2 cm^2 and 17.0 ± 9.5 cm^2, respectively. Mean TAPSE was 17.3 ± 5.1 mm. Overall, left ventricular systolic function was preserved (LVEF 53.6% ± 11.0%). Mitral regurgitation was ≥3+ in 3.3% of patients. All individuals were symptomatic, as expressed by NYHA functional class ≥ III in 89.6% of patients. Edema and ascites were observed in 65.0% and 12.1%, respectively. Detailed baseline characteristics are displayed in Table 1.

TR severity was reduced to ≤2+ in 82.4% and to ≤1+ in 48.0% of patients. At the latest available follow-up, TR remained ≤2+ in 71.9% of patients. NYHA functional class was ≤II in 56.3% of patients at follow-up (Table 2). Estimated survival rates at 1 and 2 years were 79.5% [Q1-Q3: 76.1%-83.1%] and 68.4% [Q1-Q3: 63.9%-73.3%], respectively.

Prevalence and characteristics of patients with A-STR. A-STR was observed in 30.6% of patients (n = 196). Compared with patients with nonatrial STR, those with A-STR presented with better renal function (estimated glomerular filtration rate 49.0 ± 20.0 mL/min vs 47.2 ± 23.0 mL/min; P = 0.085) and a lower prevalence of comorbidities (coronary artery disease in 39.3% vs 50.1% [P = 0.017], stroke or transient ischemic attack in 6.1% vs 14.1% [P = 0.006]). AF was more common in patients with A-STR (96.5% vs 92.0% in those with nonatrial STR; P = 0.036). Anatomically, patients with A-STR presented with smaller RV dimensions (RV end-systolic area 15.5 ± 5.3 cm^2 vs 17.6 ± 7.3 cm^2; P < 0.001) and less tenting (tenting height 7.2 ± 2.9 mm vs 7.7 ± 3.4 mm; P = 0.105). Invasive hemodynamic data suggested less pulmonary hypertension in the presence of A-STR (systolic pulmonary artery pressure 44.8 ± 11.7 mm Hg vs 48.5 ± 15.8 mm Hg [P = 0.019], pulmonary capillary wedge pressure 17.2 ± 6.3 mm Hg vs 20.1 ± 7.3 mm Hg [P < 0.001]).

T-TEER outcomes in patients with A-STR. At baseline, TR severity was statistically comparable in patients with A-STR and those with nonatrial STR (P = 0.487) (Figure 1). Postprocedurally, TR was significantly lower in patients with A-STR (TR ≤2+ in 86.9% vs 80.4% of those with nonatrial STR; P = 0.005). At the latest available follow-up, TR severity was statistically comparable between STR etiologies (TR ≤2+ in 74.8% of patients with A-STR and 70.6% of those with nonatrial STR; P = 0.353). Of note, T-TEER achieved significant improvement in TR severity from baseline to discharge and follow-up irrespective of atrial or nonatrial STR etiology (P < 0.001 for both).

TABLE 1 Study Characteristics

	All Patients (N = 641)	A-STR (n = 196)	Nonatrial STR (n = 445)	*P* Value	Data Available
Clinical characteristics					
Age, y	79.0 ± 7.1	79.6 ± 6.3	78.8 ± 7.5	0.335	641
Female	324 (50)	106 (53.5)	218 (48.4)	0.233	641
BMI, kg/cm^2	25.8 ± 4.8	26.6 ± 5.4	25.5 ± 4.4	0.034	631
EuroSCORE II	4.7 (2.6-7.5)	3.6 (2.3-5.8)	5.2 (3.0-8.3)	<0.001	621
Edema	421 (65.0)	119 (60.1)	302 (67.1)	0.085	641
Ascites	78 (12.1)	18 (9.1)	60 (13.4)	0.120	638
TRI-SCORE	7 (5-8)	7 (5-8)	7 (5-9)	0.121	439
Laboratory data					
NT-proBNP, pg/mL	4895 ± 8330	3543 ± 6761	5483 ± 8869	<0.001	610
Bilirubin, mg/dL	1.3 ± 0.8	1.2 ± 3.3	1.4 ± 4.0	0.043	539
AST, U/L	31.6 ± 13.7	31.0 ± 12.4	31.9 ± 14.3	0.477	607
ALT, U/L	21.2 ± 12.3	21.6 ± 12.9	21.0 ± 12.0	0.728	595
eGFR, mL/min	47.8 ± 22.1	49.0 ± 20.0	47.2 ± 23.0	0.085	641
Medication					
Beta-blocker	548 (84.6)	159 (80.3)	389 (86.4)	0.046	641
RAS inhibitor	310 (48.1)	91 (46.1)	219 (49.1)	0.462	637
Loop diuretic agent	596 (42.9)	174 (88.8)	422 (94.1)	0.002	638
Thiazide diuretic agent	119 (18.5)	38 (19.3)	81 (18.1)	0.725	637
MRA	283 (43.8)	82 (41.4)	201 (44.9)	0.415	639
Comorbidities					
AF/atrial flutter	605 (93.4)	191 (96.5)	414 (92.0)	0.036	641
Dyslipidemia	194 (33.2)	62 (34.4)	132 (32.7)	0.675	641
CAD	303 (47.0)	79 (39.9)	224 (50.1)	0.017	638
AHT	490 (83.8)	152 (84.4)	338 (83.5)	0.765	641
Stroke/TIA	68 (11.6)	11 (6.1)	57 (14.1)	0.006	578
Diabetes mellitus	135 (23.0)	33 (18.3)	102 (25.1)	0.072	579
COPD	109 (16.8)	32 (16.2)	77 (17.1)	0.766	641
Echocardiography					
TR vena contracta, mm	11.6 ± 4.5	11.1 ± 4.4	11.8 ± 4.8	0.122	575
TR EROA, cm^2	0.54 (0.40-0.76)	0.53 (0.40-0.74)	0.54 (0.40-0.79)	0.777	609
TR RegVol, mL	64.0 (34.0-61.0)	43.0 (34.0-59.5)	46.0 (34.0-62.0)	0.431	603
LVEF, %	53.6 ± 11.0	57.9 ± 8.3	51.8 ± 11.5	<0.001	629
LVEDD, mm	48.6 ± 8.4	47.6 ± 8.0	49.0 ± 8.5	0.023	614
Coaptation gap, mm	6.0 ± 2.9	5.8 ± 2.6	6.1 ± 3.0	0.296	467
Tenting height, mm	7.6 ± 3.2	7.2 ± 2.9	7.7 ± 3.4	0.105	549
TAPSE, mm	17.3 ± 5.1	21.4 ± 3.1	15.6 ± 4.8	<0.001	641
RVFAC, %	37.6 ± 10.8	40.8 ± 9.7	36.1 ± 10.9	<0.001	575
RVEDA, cm^2	26.9 ± 9.5	25.9 ± 8.1	27.4 ± 9.9	0.134	635
RVESA, cm^2	17.0 ± 9.5	15.5 ± 5.3	17.6 ± 7.3	0.001	635
RVmid, mm	39.3 ± 8.4	38.4 ± 7.8	39.7 ± 8.6	0.105	631
RVbase, mm	48.7 ± 9.1	48.5 ± 9.2	48.7 ± 9.1	0.796	629
TV annular diameter, mm	44.7 ± 9.0	45.2 ± 8.7	44.5 ± 9.1	0.293	635
RA area, mm^2	36.9 ± 12.2	37.5 ± 11.9	36.6 ± 12.3	0.410	635
Echocardiographic sPAP, mm Hg	41.2 ± 14.0	41.2 ± 12.9	41.2 ± 14.5	0.785	619
Right heart catheterization					
sPAP, mm Hg	47.4 ± 15.0	44.8 ± 11.7	48.5 ± 15.8	0.019	500
dPAP, mm Hg	19.9 ± 7.6	18.5 ± 6.8	20.5 ± 7.9	0.013	464
mPAP, mm Hg	30.6 ± 9.6	28.9 ± 8.3	31.4 ± 10.1	0.011	499
PCWP, mm Hg	19.3 ± 7.2	17.2 ± 6.3	20.1 ± 7.3	<0.001	395

Values are mean ± SD, n (%), or median (Q1-Q3). Percentages refer to eligible patients.

AF = atrial fibrillation; AHT = arterial hypertension; ALT = alanine aminotransferase; AST = aspartate aminotransferase; A-STR = atrial secondary tricuspid regurgitation; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; dPAP = diastolic pulmonary artery pressure; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary artery pressure; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-brain natriuretic peptide; PCWP = pulmonary capillary wedge pressure; RA = right atrial; RAS = renin-angiotensin system; RegVol = regurgitant volume; RVbase = right ventricular basal diameter; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; RVFAC = right ventricular fractional area change; RVmid = right ventricular midventricular diameter; sPAP = systolic pulmonary artery pressure; STR = secondary tricuspid regurgitation; TAPSE = tricuspid annular plane systolic excursion; TIA = transient ischemic attack; TR = tricuspid regurgitation; TV = tricuspid valve.

NYHA functional class at baseline was comparable in patients with A-STR and those with nonatrial STR ($P = 0.874$). T-TEER improved NYHA functional class for both etiologies ($P < 0.001$ for both), with more severe NYHA functional class at follow-up in patients with nonatrial STR (NYHA functional class ≥ III in 46% of patients with nonatrial STR vs 38% of those with A-STR; $P = 0.033$) (**Figure 2**).

One- and 2-year survival rates were higher in patients with A-STR compared with those with nonatrial STR (1 year: 84.0% [Q1-Q3: 78.3%-90.1%] vs 77.6% [Q1-Q3: 73.5%-82.0%]; 2 years: 79.3% [Q1-Q3: 72.5%-86.8%] vs 63.8% [Q1-Q3: 58.1%-70.0%]; $P < 0.001$) (**Figure 3**). The same applied for a combined endpoint of survival free from HHF (1 year: 77.0% [Q1-Q3: 70.5%-84.1%] vs 65.8% [Q1-Q3: 61.1%-70.8%]; 2 years: 66.3% [Q1-Q3: 58.2%-75.5%] vs 47.5% [Q1-Q3: 41.7%-54.2%]; $P < 0.001$ for both) (**Central Illustration**). Median survival follow-up was 379 days [Q1-Q3: 155-697 days]. Within the first 2 years after T-TEER, 11.1% of patients with A-STR and 16.7% of those with nonatrial STR were hospitalized for heart failure. Of note, after adjustment for potential confounders in a multivariable Cox regression model, A-STR was an independent predictor of 2-year survival free from HHF (HR: 0.650; 95% CI: 0.446-0.946; $P = 0.025$) (**Table 3**, Supplemental Tables 1 and 2). A-STR was confirmed as a multivariable outcome predictor in an additional theory-driven Cox regression model (Supplemental Table 3). Supplemental Figure 2 provides Kaplan-Meier charts comparing 2-year survival free from HHF in patients with A-STR vs nonatrial STR with a transtricuspid lead vs nonatrial STR without a transtricuspid lead vs primary TR. In addition, Supplemental Table 4 gives an overview of residual TR and the number of implanted devices within the aforementioned subetiologies of TR.

TABLE 2 Study Outcomes

	All Patients	A-STR	Nonatrial STR	*P* Value
TR severity				0.487
1+	0 (0.0)	0 (0.0)	0 (0.0)	
2+	21 (3.2)	8 (4.0)	13 (2.9)	
3+	309 (47.7)	93 (47.0)	216 (48.0)	
4+	197 (30.4)	67 (33.8)	130 (28.9)	
5+	121 (18.7)	30 (15.2)	91 (20.2)	
TR severity at discharge				0.005
1+	303 (48.0)	107 (56.0)	196 (44.5)	
2+	217 (34.4)	59 (30.9)	158 (35.9)	
3+	89 (14.1)	20 (10.5)	69 (15.7)	
4+	16 (2.5)	2 (1.0)	14 (3.2)	
5+	6 (1.0)	3 (1.6)	3 (0.7)	
TR severity at follow-up				0.353
1+	119 (29.3)	41 (31.3)	72 (28.4)	
2+	173 (42.6)	57 (43.5)	116 (42.2)	
3+	88 (21.7)	25 (19.1)	63 (22.9)	
4+	16 (3.9)	6 (4.6)	10 (3.6)	
5+	10 (2.5)	2 (1.5)	8 (2.9)	
NYHA functional class at baseline				0.874
I	5 (0.8)	2 (1.0)	3 (0.7)	
II	62 (9.6)	16 (8.1)	46 (10.2)	
III	479 (73.9)	152 (76.8)	327 (72.2)	
IV	102 (15.7)	28 (14.1)	74 (16.4)	
NYHA functional class at follow-up				0.033
I	49 (11.6)	23 (16.9)	26 (9.1)	
II	189 (44.7)	61 (44.9)	128 (44.6)	
III	154 (36.4)	44 (32.4)	110 (38.3)	
IV	31 (7.3)	8 (5.9)	23 (8.0)	

Values are n (%).
Abbreviations as in **Table 1**.

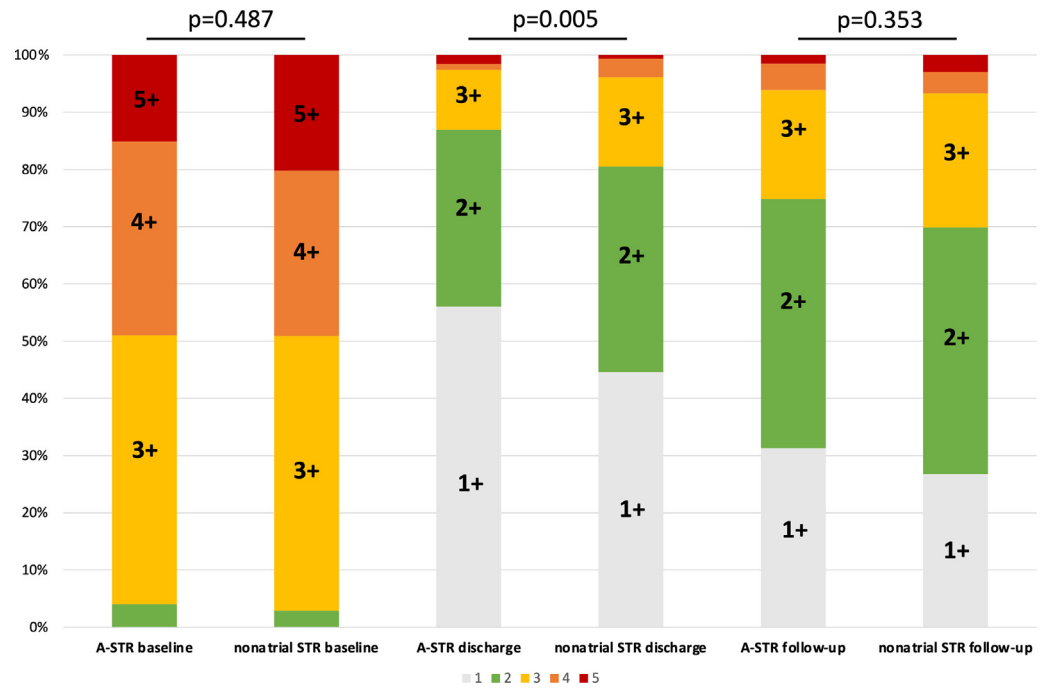
DISCUSSION

GENERAL CONSIDERATIONS. The present analysis reports the prevalence and outcomes of A-STR in the by far largest available contemporary cohort of patients with TR treated exclusively using T-TEER. The main findings (**Central Illustration**) of this analysis were as follows: 1) A-STR was prevalent in 30% of patients in a real-world T-TEER cohort; 2) A-STR was associated with lower residual TR at discharge; 3) patients with A-STR had higher rates of 1- and 2-year survival free from HHF; and 4) patients with A-STR had better symptomatic improvement at follow-up.

A-STR, as defined in this study, is characterized by excessive RA dilation while maintaining preserved RV dimensions and function, aligning with the TVARC consensus statement and a recent state-of-the-art paper.[14,15] Despite the comprehensive parameters proposed in the consensus paper, the complexity of everyday clinical practice, marked by challenging echocardiographic conditions and overlapping phenotypes, necessitates a practical definition. Although being aligned to the TVARC recommendations, the chosen A-STR definition in this study is based on practical, major routine echocardiographic data emphasizing preserved RV function and disproportionate RA dilatation in relation to the RV.

BASELINE DIFFERENCES BETWEEN A-STR AND NONATRIAL STR. Patients with A-STR were approximately 2 years younger compared with those presenting with nonatrial STR, further strengthening distinct differences in the pathophysiology of both subtypes. Patients with A-STR presented with lower surgical risk (European System for Cardiac Operative Risk Evaluation II score 5.0% vs 6.5% and TRI-SCORE 6.5 points vs 6.8 points, respectively), probably because of less frequent comorbidities (stroke or

FIGURE 1 Changes in TR Following Transcatheter Tricuspid Valve Edge-to-Edge Repair in Patients With A-STR vs Nonatrial STR



Baseline tricuspid regurgitation (TR) severity was comparable in patients with atrial secondary TR (A-STR) and nonatrial secondary TR (STR). At discharge, TR remained more severe in patients with nonatrial STR, a trend that was also observed at the latest follow-up.

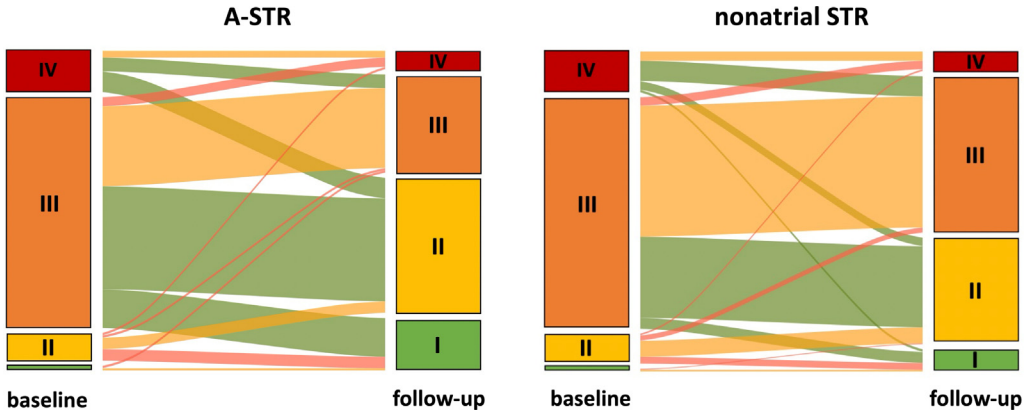
transient ischemic attack, diabetes, and the cardiorenal syndrome) and less advanced biventricular heart failure. These differences are also reflected by a lower TRI-SCORE in patients with A-STR compared with nonatrial STR. In concordance with the TVARC consensus statement,[14] A-STR was associated with a more favorable invasive hemodynamic profile on the basis of right heart catheterization (lower mean pulmonary artery pressure and pulmonary capillary wedge pressure), most likely because of less frequent left heart involvement and pulmonary hypertension.

Observing a statistically significant higher prevalence of AF in the setting of A-STR compared with nonatrial STR supports the hypothesis that AF (especially nonparoxysmal AF)[15] might be a major driver of A-STR, which has previously been reported.[19] Differentiation of paroxysmal, persistent, and permanent AF might be important for future research to obtain further insights into the exact underlying pathomechanisms. The patient cohort studied in this analysis presented in an advanced stage of right heart disease, probably with long-standing persistent or permanent AF. Attempting rhythm control early within the disease process either by pulmonary vein isolation or medically might decelerate the progression of A-STR. Dedicated longitudinal studies are needed to confirm the potential relationship of AF and A-STR and to uncover the potential impact of rhythm control on progression of A-STR.

In the context of severe TR, the presence of AF seemed be associate with better outcomes compared with those presenting with sinus rhythm (multivariate predictor in a theory-driven Cox regression analysis; see Supplemental Table 3). This once again mirrors the phenotypic heterogeneity of TR and might reflect differences of patients with A-STR vs nonatrial STR regarding pathophysiology and comorbidities. However, it is important to keep in mind that this association of AF and better outcomes is observed in a highly selected patient cohort.

THE ROLE OF A-STR IN RANDOMIZED TRIALS. A-STR came into scientific focus after the first and only

FIGURE 2 NYHA Functional Class After Transcatheter Tricuspid Valve Edge-to-Edge Repair Stratified by A-STR and Nonatrial STR

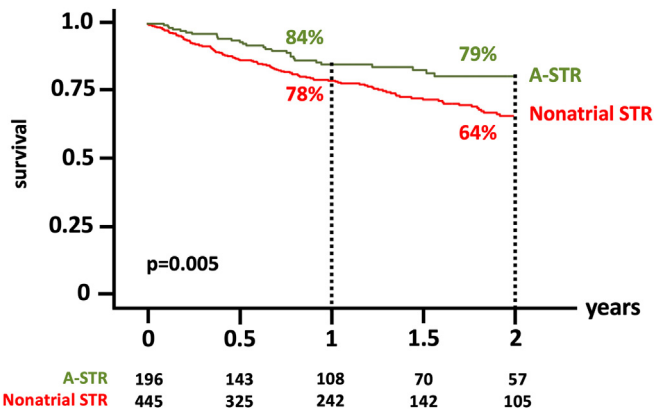


NYHA functional class significantly improved following transcatheter tricuspid valve edge-to-edge repair, irrespective of TR subetiology. However, although comparable at baseline, NYHA functional class indicated more severe heart failure symptoms at follow-up in patients with nonatrial STR. Abbreviations as in Figure 1.

currently available trial in the field of T-TEER (TRILUMINATE) was designed.[7] The patient population treated in this trial was considered to have "isolated" TR,[20,21] a term which has been used previously to describe TR without relevant cardiac comorbidities. A-STR characteristics in this study hint at its potential predominance in a substantial subset of trial patients. Nevertheless, a dedicated substudy that differentiates both phenotypes within the trial population is pending. As we have learned from the field of secondary mitral regurgitation, an etiologic and phenotypic work-up of patients is crucial for understanding treatment response and thus outcomes. Future T-TEER trials should consider TR etiology to comprehensively understand treatment response and outcomes in the context of interventional treatment.

TVARC CRITERIA, REAL-WORLD DISCREPANCIES, AND DISEASE PROGRESSION. As mentioned earlier, the TVARC consensus statement offers a variety of morphologic, echocardiographic, and hemodynamic parameters to differentiate A-STR from nonatrial STR on the basis of the current body of evidence in the field of A-STR.[14,22-24] Even though the proposed cut-offs provide a very sharp distinction between both phenotypes, the large variety of parameters makes application in everyday clinical practice challenging. A-STR is a rather dynamic process likely able to progress and develop ventricular involvement with RV dilation and deterioration of RV function. In a real-world setting, patients with "isolated" A-STR and those with nonatrial STR meeting all TVARC criteria are rarely encountered, especially as with progressing disease stages, overlapping phenotypes may occur. Therefore, the TVARC A-STR criteria are met only in a certain percentage of patients (tenting height ≤9 mm in 82%, fractional area change ≥35% in 75%) (Table 4). Longitudinal studies are urgently needed to gain further insights into the natural history of A-STR. This is probably of special interest in early disease states, when rhythm control in patients

FIGURE 3 2-Year Survival After Transcatheter Tricuspid Valve Edge-to-Edge Repair in Patients With A-STR and Nonatrial Secondary Tricuspid Regurgitation



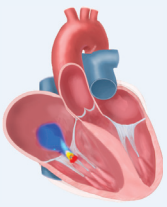
A-STR was associated with a trend toward better 2-year survival following transcatheter tricuspid valve edge-to-edge repair. V-STR = ventricular secondary tricuspid regurgitation.

CENTRAL ILLUSTRATION Atrial Secondary Tricuspid Regurgitation in the EuroTR Registry

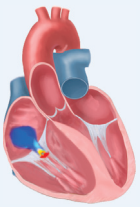
EuroTR Registry: Transcatheter Edge-to-Edge Repair in Patients With Secondary Tricuspid Regurgitation, N = 641

Patient Population

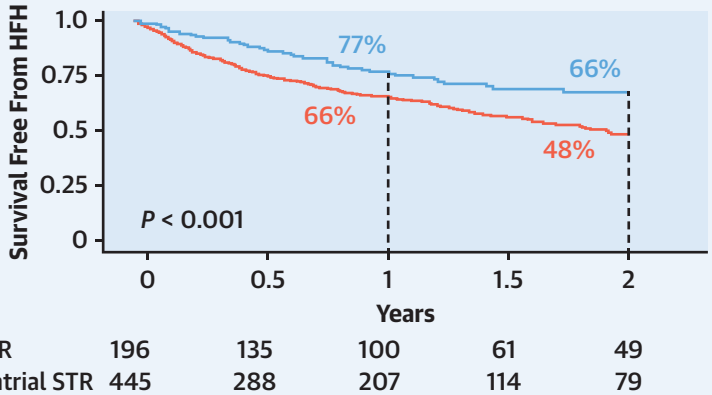
- 50% women
- Mean age 79 ± 7 years
- Increased surgical risk
  - EuroScore II 6.0% ± 5.3%
  - TRI-SCORE 6.7 ± 2.1 points
- Progressive heart failure
  - NYHA functional class III or IV 90%
  - Peripheral edema 65%
  - Ascites 12%



Atrial Secondary TR	Case distribution	Nonatrial Secondary TR
31%		69%
≥1.5	RA/RV area ratio	<1.5
>17 mm	TAPSE	≤17 mm



Survival Free From HF Hospitalization



- Atrial secondary TR is a common phenotype of secondary TR and is associated with effective TR reduction and symptomatic improvement after TEER
- Survival free from HF hospitalization was higher in patients with atrial secondary TR than in those with nonatrial secondary TR (77.0% vs 65.8% at 1 year; 66.3% vs 47.5% at 2 years, $P < 0.001$ for both)
- Atrial secondary TR was an independent predictor of 2-year survival free from HF hospitalization (HR: 0.65, 95% CI: 0.45-0.95, $P = 0.025$)

Stolz L, et al. JACC Cardiovasc Interv. 2024;17(23):2781-2791.

A-STR = atrial secondary tricuspid regurgitation; EuroScore = European System for Cardiac Operative Risk Evaluation; EuroTR = European Registry of Transcatheter Repair for Tricuspid Regurgitation; HF = heart failure; RA = right atrial; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TEER = transcatheter edge-to-edge repair; TR = tricuspid regurgitation; V-STR = ventricular secondary tricuspid regurgitation.

with AF might prevent disease progression and thus improve TR, as observed with atrial secondary mitral regurgitation.[12] Similarly, it will be important to understand whether conditions such as cardiac amyloidosis are causally involved in the development of heart failure with preserved ejection fraction to be able to interpret outcome data of clinical T-TEER studies more differentially.[25]

Beyond that and in contrast to previously published literature on A-STR, we did not include tenting

height and/or area in our A-STR definition. We believe that differences in valve anatomy are attributable primarily to changes that are the result of excessive RA dilation against the background of preserved RV dimensions and function. This is confirmed by the fact that according to the A-STR definition proposed in this paper, patients with A-STR and those with nonatrial STR present with significant differences in the extent of tricuspid valve tenting.

Future trials in the field of transcatheter tricuspid valve repair and replacement should try to comprehensively assess TR etiology by following the TVARC consensus statement recommendations. Data derived from such (randomized controlled) prospective studies might help produce further insights into the pathophysiology of different TR etiologies and generalizability of simplified A-STR definitions in everyday clinical practice. In the best case, those trials should be powered to assess treatment effects within each subetiology of TR.

PROGNOSTIC IMPLICATIONS OF A-STR. In our cohort of real-world T-TEER patients, we observed an association of A-STR with more distinct TR reduction compared with nonatrial STR (TR ≤2+ in 86.9% vs 80.4). Although having comparable gap sizes, leaflet tenting was significantly more pronounced in the presence of nonatrial STR, which might have led to slightly lower rates of procedural success.[26] Indeed, leaflet tenting was previously identified as a predictor of procedural failure in the TriValve registry.[26] A similar trend was observed in previous studies[23] with overall slightly lower procedural success compared with our registry. Beyond that, patients with nonatrial STR had larger left ventricular and RV dimensions. Nonetheless, growing experience of imagers, interventionalists, and heart teams as a crucial part in the decision process prior to T-TEER might improve outcomes in the future. Until today, dedicated analyses on the impact of operator experience and site volume in terms of T-TEER are missing. With the recent Conformité Européenne (CE) mark approval of the EVOQUE transcatheter tricuspid valve replacement system (Edwards Lifesciences), another device became available for patients being considered suboptimal candidates for TEER. Transcatheter annuloplasty has been shown to be associated with more pronounced TR reduction in patients with atrial compared with ventricular TR.[27] Data comparing the performance of annuloplasty vs TEER in A-STR are missing. Further studies are needed to guide patient and device selection in the versatile landscape of TR. In terms of symptomatic outcomes, A-STR was associated with a significantly higher percentage of patients presenting in NYHA functional class I at 1-year follow-up. Of note, substantial symptomatic relief was observed irrespective of STR subetiology. Finally, as previously described, patients with A-STR presented with lower rates of 1-year survival free from HHF,[22,23] which was confirmed in a multivariable Cox regression model. Besides A-STR, history of stroke, and left ventricular end-diastolic diameter, male sex was an independent predictor of death or HHF at 1 year. This is an interesting finding, as previous studies in the field of interventional TR treatment did not reveal an association of sex and outcomes after T-TEER. An analysis from the TriValve registry (which included not only T-TEER patients but also patients undergoing different other device therapies) reported equal treatment effects in men and women.[28] Further studies are needed to give in-depth insights into potentially sex-related differences in pathomechanisms of TR and the respective interventional, conservative, and surgical treatment response.

As previously reported for patients with high-risk TR, overall LVEF was preserved (52.6% ± 11.4%).

TABLE 3 Cox Regression Model (2-Year Mortality or Heart Failure Hospitalization)

	Univariate			Multivariable		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Male	1.611	1.220-2.127	<0.001	1.709	1.199-2.435	0.003
A-STR	0.564	0.405-0.784	<0.001	0.650	0.446-0.946	0.025
Stroke/TIA	1.708	1.111-2.626	0.015	1.708	1.111-2.626	0.015
LVEDD	1.025	1.003-1.047	0.023	1.025	1.003-1.047	0.023

Abbreviations as in Table 1.

TABLE 4 TVARC Criteria in EuroTR

Tenting height ≤9 mm	81.6 (408/549)
RVmid diameter ≤38 mm	52.0 (310/631)
End-systolic RA/RV ratio ≥1.5	100 (545/641)
TASPE >17 mm	100 (292/641)
RVFAC ≥35%	74.9 (351/575)
PCWP ≤15 mm Hg	42.5 (126/395)

Values are percentage of A-STR patients meeting the criterion (n/N).
RV = right ventricular; RVFAC = right ventricular fractional area change; other abbreviations as in Table 1.

Probably as a result of lacking heterogeneity in left ventricular function within the limited study cohort, LVEF was not a significant outcome predictor in the Cox regression model. Findings were comparable for left ventricle dimensions when focusing on 2-year mortality (Supplemental Table 2).

With rising awareness for the etiologic heterogeneity of TR, the body of evidence regarding A-STR is expected to grow rapidly within the coming years. As mentioned earlier, comparative studies assessing potential differences in treatment response of A-STR to T-TEER vs annuloplasty vs surgical or medical management are urgently needed. Given its extraordinarily high safety profile and effective rates of TR reduction, T-TEER currently seems a reasonable treatment approach for patients with A-STR.

STUDY LIMITATIONS. Despite including the largest cohort of T-TEER-treated patients with A-STR, the study lacked echocardiographic core laboratory supervision. The study might be subject to a certain selection bias, as patients with missing information on TAPSE and RA and RV size were excluded. Not all anatomical parameter listed in the TVARC consensus document are available within the EuroTR registry. Because of the retrospective design of this registry, we have no longitudinal data available on the progression of TR over time. Therefore, we cannot rule out that the group of patients with nonatrial STR contained a certain number of patients with A-STR in a very late disease stage. The EuroTR registry included patients with CIED leads across the tricuspid valve. However, information regarding the specific contribution of each lead to TR were not registered.

CONCLUSIONS

Among a real-world cohort of T-TEER-treated patients with TR, A-STR was prevalent in 30% of patients. A-STR was associated with less residual TR, better symptomatic reduction, and improved survival following T-TEER. To gain a more comprehensive understanding of A-STR and its possible implications for treatment response and prognosis, future randomized controlled studies should incorporate detailed assessment of STR subtypes.

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Dr Stolz has received speaker honoraria from Edwards Lifesciences. Dr Kresoja has received travel expenses from Edwards Lifesciences. Dr von Stein has received lecture honoraria from Edwards Lifesciences. Dr Rottbauer has received speaker honoraria Edwards Lifesciences and Abbott. Der Denti has served as a consultant for InnovHeart, Pi-Cardia, HVR, and Approxima; and has received speaker honoraria from Abbott and Edwards Lifesciences. Dr Rassaf has received speaker honoraria and consulting fees from AstraZeneca, Bayer, Pfizer, and Daiichi-Sankyo. Dr Barreiro-Perez has received speaker fees from Abbott Vascular, Edwards Lifesciences, and Venus Medtech. Dr Adamo has received consulting fees in the past 3 years from Abbott Structural Heart and Edwards Lifesciences. Dr von Bardeleben has received institutional grants from and served as a speaker for Abbott Vascular and Edwards Lifesciences. Dr Toggweiler has received personal honoraria from Medtronic, Boston Scientific, Biosensors, Abbott Vascular, Medira, Shockwave Medical, Teleflex, atHeart Medical, Cardiac Dimensions, Polares Medical, Amarin, Sanofi, AstraZeneca, ReCor Medical, and Daiichi-Sankyo; has received institutional research grants from Edwards Lifesciences, Boston Scientific, Fumedica, Novartis, and Boehringer Ingelheim; and holds equity in Hi-D Imaging. Dr Metra has received consulting fees in the past 3 years from Abbott Structural Heart, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, and Roche Diagnostics. Dr Geisler has received speaker honoraria and research grants from AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Ferrer/Chiesi, Medtronic, and Edwards Lifesciences (all unrelated to this study). Dr Estévez-Loureiro has received speaker fees from Abbott Vascular, Edwards Lifesciences, Boston Scientific, and Venus Medtech. Dr Lüdike has received speaker honoraria and consulting fees from AstraZeneca, Bayer, Pfizer, and Edwards Lifesciences; and has received research honoraria from Edwards Lifesciences. Dr Maisano received grant and/or research institutional support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific, NVT, Terumo, and Venus Medtech; has received consulting fees and personal and institutional honoraria from Abbott, Medtronic, Edwards Lifesciences, Xeltis, Cardiovalve, Occlufit, Simulands, Mtex, Venus, Squadra, and Valgen; has received royalty income from and holds intellectual property rights with Edwards Lifesciences; and is a shareholder (including share options) in Magenta, Transseptal Solutions, and 4Tech. Dr Praz has received travel expenses from Edwards Lifesciences, Abbott Vascular, Polares Medical, Medira, and Siemens Healthineers. Dr Kessler has received speaker honoraria from Edwards Lifesciences and Abbott. Dr Kalbacher has received personal fees from Abbott Medical, Edwards Lifesciences, Pi-Cardia, and Medtronic. Dr Rudolph has received research grants from Abbott Medical, Boston Scientific, and Edwards Lifesciences. Dr Iliadis has received consultant fees and travel expenses from Abbott Medical and Edwards Lifesciences. Dr Lurz has received institutional grants from Edwards Lifesciences; and has received honoraria from Inoventrics. Dr Hausleiter has received research grant support and speaker honoraria from Edwards Lifesciences. Dr Sticchi has served on an advisory board for Edwards Lifesciences. Dr Tarantini has received speaker fees from Abbott Vascular and Edwards Lifesciences. Dr Karam has received consultant fees from Edwards Lifesciences, Boston Scientific, and Medtronic; and has received proctor fees from Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? TR is a heterogenous disease entity.

WHAT IS NEW? According to an echocardiographically based definition (ratio of RA area to RV area ≥1.5 and TAPSE >17 mm) of A-STR was prevalent in 31% of patients undergoing T-TEER for relevant TR. The etiologic differentiation of atrial and nonatrial TR yielded prognostic value.

WHAT IS NEXT? Randomized trials are needed to shed further light into potential differences in treatment response of different TR phenotypes with regard to medical, surgical, and interventional therapy.

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KEY WORDS atrial fibrillation, atrial secondary tricuspid regurgitation, functional secondary tricuspid regurgitation, T-TEER

APPENDIX For supplemental tables and figures as well as a list of EuroTR investigators, please see the online version of this paper.