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6-Month Outcomes of Tricuspid Valve Reconstruction for Patients With Severe Tricuspid Regurgitation

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ABSTRACT

BACKGROUND Severe tricuspid regurgitation (TR) is associated with high morbidity and mortality rates with limited treatment options.

OBJECTIVES The authors report the 6-month safety and performance of a transcatheter tricuspid valve reconstruction system in the treatment of moderate to severe functional TR in 30 patients enrolled in the TRI-REPAIR (TrIcuspid Regurgitation RePAIr With CaRdioband Transcatheter System) study.

METHODS Between October 2016 and July 2017, 30 patients were enrolled in this single-arm, multicenter, prospective trial. Patients were diagnosed with moderate to severe, symptomatic TR in the absence of untreated left-heart disease and deemed inoperable because of unacceptable risk for open-heart surgery by the local heart team. Clinical, functional, and echocardiographic data were prospectively collected before and up to 6 months post-procedure. An independent core lab assessed all echocardiographic data, and an independent clinical event committee adjudicated the safety events.

RESULTS Mean patient age was 75 years, 73% were female, and 23% had ischemic heart disease. At baseline, 83% were in New York Heart Association (NYHA) functional class III to IV, and mean left ventricular ejection fraction was 58%. Technical success was 100%. Through 6 months, 3 patients died. Between 6 months and baseline, echocardiography showed average reductions of annular septolateral diameter of 9% (42 mm vs. 38 mm; $p < 0.01$), proximal isovelocity surface area effective regurgitant orifice area of 50% (0.8 cm^2 vs. 0.4 cm^2; $p < 0.01$), and mean vena contracta width of 28% (1.2 cm vs. 0.9 cm; $p < 0.01$). Clinical assessment showed that 76% of patients improved by at least 1 NYHA functional class with 88% in NYHA functional class I or II. Six-minute walk distance improved by 60 m ($p < 0.01$), and Kansas City Cardiomyopathy Questionnaire score improved by 24 points ($p < 0.01$).

CONCLUSIONS Six-month outcomes show that the system performs as intended and appears to be safe in patients with symptomatic and moderate to severe functional TR. Significant reduction of TR through decrease of annular dimensions, improvements in heart failure symptoms, quality of life, and exercise capacity were observed. Further studies are warranted to validate these initial promising results. (TrIcuspid Regurgitation RePAIr With CaRdioband Transcatheter System [TRI-REPAIR]; NCT02981953) (J Am Coll Cardiol 2019;73:1905–15) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CT = computed tomography

EROA = effective regurgitant orifice area

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

MSAE = major serious adverse event

NYHA = New York Heart Association

PISA = proximal isovelocity surface area

RCA = right coronary artery

RV = right ventricular

TR = tricuspid regurgitation

Tricuspid regurgitation (TR) is frequent, and its prevalence is similar to aortic stenosis and represents one-fourth of all left-sided valve-related diseases (1). It has been estimated that approximately 1.6 million individuals in the United States and more than 3 million in Europe have clinically relevant TR (2). TR is rarely caused by congenital or acquired damage of the leaflets and valvular apparatus. Approximately 80% to 90% of TR is functional TR, secondary to abnormal cardiac function. In a large study of 63,472 consecutive patients referred for transthoracic echocardiography, severe TR was identified in 1.2% of patients (3). Functional TR is most commonly associated with pulmonary hypertension and/or left-sided heart disease. Moderate to severe right ventricular (RV) enlargement or RV dysfunction was present in 28% and 18% of patients, respectively. In addition, chronic atrial fibrillation is increasingly reported as a cause of TR, and persistent atrial fibrillation causing right atrial and RV dilatation frequently predisposes to TR (1–5).

The negative clinical impact of TR has been reported for various patient groups. One of the largest observational studies of 5,223 ambulatory patients in the U.S. Veteran's Health Administration demonstrated that increased severity of TR was associated with poor survival (6). In contrast to former reasoning, studies in mitral regurgitation patients treated with the edge-to-edge technique revealed that TR persisted in 67% of patients despite appropriate treatment of left-sided valvular disease (7). In addition, despite successful treatment of mitral regurgitation, higher morbidity and mortality rates are experienced in patients with concomitant TR (7–13).

Medical therapy for TR is limited to the use of diuretics for systemic congestion and pharmacological treatment of hypertension, atrial fibrillation, and heart failure. Timing and value of tricuspid surgery for TR remains controversial in the absence of randomized trials, and therefore, guideline level of evidence is based on consensus of expert opinions (3,4). In patients with functional TR, surgical tricuspid repair concomitant with left-sided surgery does not increase operative risk and is associated with reverse remodeling of the RV and improvement of functional status. However, isolated surgery for persistent TR after previous left-heart surgery carries a perioperative mortality risk as high as 20% (1–5,14).

Minimally invasive catheter-based procedures could potentially reduce TR with lower periprocedural risk and improve the patient's clinical status and prognosis. In recent years, different technologies have been described, of which a few are being evaluated in prospective clinical trials (15–19). Because annular dilatation is the central pathology in most patients with TR, devices that aim to reduce tricuspid annular dimensions are of particular interest.

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Previously, the Cardioband system (Edwards Lifesciences, Irvine, California) has been successful in patients for reduction of functional mitral regurgitation (20). With limited iterations, the system has been applied to the tricuspid space. We report the 6-month follow-up results from the international, multicenter, and prospective TRI-REPAIR (TrIcuspid Regurgitation RePAIr With CaRdioband Transcatheter System)

Medtronic, Novartis, Pfizer, Sanofi, and St. Jude Medical; and has participated in clinical trials for Abbott, AGA Medical, AstraZeneca, Bayer, Berlin Chemie, Biosensus, Biotronic, Bristol-Myers Squibb, Boehringer Ingelheim, Cardiovalve, Daiichi-Sankyo, Edwards Lifesciences, Medtronic, Novartis, Pfizer, Sanofi, and St. Jude Medical. Dr. Schueler has received speaker honoraria from Edwards Lifesciences. Dr. Hausleiter has received research support and honoraria from Abbott Vascular and Edwards Lifesciences. Dr. Näbauer has received lecture fees and served on an advisory board for Abbott Vascular. Dr. Schäfer has received speaker honoraria as well as travel and grant support from Edwards Lifesciences. Dr. Deuschl has been a consultant and received speaker honoraria as well as travel and grant support from Edwards Lifesciences; has been a proctor for Cardioband and Edwards Lifesciences; and has been an employee of Edwards Lifesciences. Dr. Kuck has been a consultant for Medtronic, Abbott, Boston Scientific, Edwards Lifesciences, and Biosense Webster. Dr. Kreidel has received speaker honoraria from Valtech and Edwards Lifesciences. Dr. Brochet has received proctoring fees from Abbott. Dr. Latib has served on advisory boards for Medtronic and Abbott; and has been a consultant to Edwards Lifesciences. Dr. Agricola has received speaker honoraria from Edwards Lifesciences. Dr. Baldus has received speaker honoraria as well as travel and grant support from Edwards Lifesciences. Dr. Vandrangi is an employee of Edwards Lifesciences. Dr. Verta is an employee of and holds stock in Edwards Lifesciences. Dr. Hahn has been a speaker for Abbott Vascular, Boston Scientific, Bayliss, Edwards Lifesciences, Philips Healthcare, and Siemens Healthineers; has served as a consultant/on advisory boards for 3Mensio, Abbott Vascular, Edwards Lifesciences, GE Healthcare, Gore & Associates, Medtronic, Navigate, Philips Healthcare, and Siemens Healthineers; and has served as chief scientific officer for the echocardiography core laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored trials for which she receives no direct industry compensation. Dr. Maisano has been a consultant for and received institutional grants from Valtech Cardo and for Edwards Lifesciences; is a shareholder of Valtech Cardo; and receives royalties from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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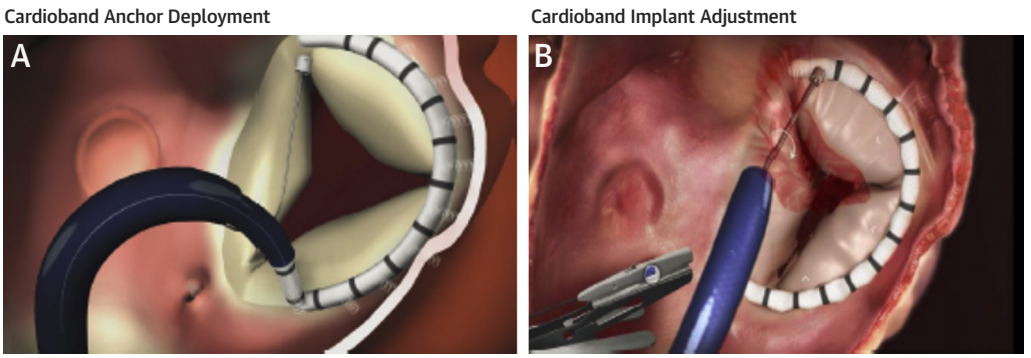
FIGURE 1 The Tricuspid Valve Reconstruction System



(A) Anchor deployment through implant to the tissue. **(B)** Adjustment of implant. Image provided by Edwards Lifesciences.

study assessing safety and performance of the Cardioband transcatheter tricuspid valve reconstruction system for the treatment of functional TR.

METHODS

TRIAL DESIGN AND PATIENTS. The TRI-REPAIR study is a single-arm, international, multicenter, prospective trial. We herein report data for the enrolled 30 patients. Eight European centers were activated in this study. Key inclusion criteria included: symptomatic, chronic, functional TR, moderate to severe TR with annular diameter ≥40 mm as reported by the study sites, stable medical treatment, and exclusion from surgery by the local heart team. Patients with left ventricular ejection fraction (LVEF) <30% and recent myocardial infarction or known unstable angina within 30 days before the index procedure were excluded. Other main exclusion criteria included: systolic pulmonary pressure > 60 mm Hg; aortic, mitral, and/or pulmonic valve stenosis and/or regurgitation moderate or severe; previous tricuspid valve repair or replacement; presence of transtricuspid pacemaker or defibrillator leads impinging the tricuspid valve leaflet as evaluated by echocardiography; any percutaneous coronary intervention or transcatheter valvular intervention within 30 days before the index procedure or planned 3 months post-index procedure; chronic dialysis and/or anemia (hemoglobin <9 g/dl); life expectancy of <12 months; or presence of cardiac cachexia.

The anatomical feasibility for device implantation was assessed by transthoracic and transoesophageal echocardiography, and by cardiac computed tomography (CT). Cardiac CT scan was used to size the tricuspid annulus for implant length selection and to plan the procedure (mitigating the risk of injury to the right coronary artery [RCA] and generating planning views). The implant size was chosen according to the pre-operative measurements of the tricuspid annulus length using cardiac CT scan at maximal diastolic opening of the valve. When available, 3-dimensional reconstructive modalities such as multiplanar echocardiography and echocardiographic-fluoroscopic fusion were used.

The TRI-REPAIR study was conducted in conformity with the ethical principles set forth by the Declaration of Helsinki, Good Clinical Practice principles, and in accordance with ISO 14155:2011. The study was approved by local ethics committees and respective health authorities of the participating countries. All patients provided written informed consent. The study is registered at ClinicalTrials.gov (NCT02981953).

THE TRANSCATHETER TRICUSPID ANNULAR REDUCTION SYSTEM. The tricuspid implant is a transcatheter tricuspid valve repair device designed to reduce TR via annular reduction. The transcatheter tricuspid system accesses the tricuspid valve via a transfemoral venous approach. The delivery system is steered until the tip of the implantation catheter is securely placed in the anterior-septal commissure area. The implant, which consists of a contraction wire and polyester fabric covering with radiopaque markers attached to an adjustment mechanism, is affixed along the annulus of the valve using a series of anchors.

THE TRANSCATHETER IMPLANTATION PROCEDURE. The implant is secured in the optimal position along the anterior portion of the tricuspid valve annulus by deploying a series of anchors in a stepwise manner (Figure 1A), while using echocardiography and fluoroscopy guidance to verify proper placement. Implantation of the tricuspid implant starts in the

TABLE 1 Baseline Characteristics of the Study Population (N = 30)

Age, yrs	75.2 ± 6.6
Female	22 (73.3)
EuroSCORE II	4.1 ± 2.8
STS score	2.6 ± 1.6
NYHA functional class III or IV	25 (83.3)
TR etiology	
Functional	30 (100)
Comorbidities	
Systemic hypertension	24 (80.0)
Elevated pulmonary pressure (>35 mm Hg)	15 (50.0)
Diabetes	8 (26.7)
Dyslipidemia	16 (53.3)
Chronic renal disease	16 (53.3)
Atrial fibrillation/flutter	28 (93.3)
Ablation for atrial fibrillation/flutter	6 (20.0)
Ventricular tachycardia/fibrillation	2 (6.7)
Coronary artery disease	11 (36.7)
Congestive heart failure	17 (56.7)
Prior stroke/transient ischemic attack	5 (16.7)
Prior left-sided heart surgery	4 (13.3)
Prior left-sided transcatheter valve replacement or repair	3 (10.0)
Coronary artery bypass graft	7 (23.3)
Percutaneous coronary intervention	6 (20.0)
Prior LAA closure	2 (6.7)
Prior PFO closure	1 (3.3)
Prior carotid surgery	1 (3.3)
Prior pacemaker/ICD/CRT	4 (13.3)

Values are mean ± SD or n (%).

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; LAA = left atrial appendage; MI = myocardial infarction; NYHA = New York Heart Association; PFO = patent foramen ovale; STS = Society of Thoracic Surgeons; TR = tricuspid regurgitation.

anterior-septal commissure area and is advanced along the anterior annulus to the posterior annulus. After the implant is fully deployed, the size-adjustment tool is introduced over a wire and contracts the pre-mounted wire of the implant. The size-adjustment tool contracts the entire implant, thus reducing the tricuspid annular diameter. Reduction in TR is assessed in real time by echocardiographic guidance under beating heart conditions (**Figure 1B**). When the appropriate amount of TR reduction has been achieved, the implant is detached from the delivery system, which is then removed.

TRIAL ENDPOINTS. The primary performance endpoint for the TRI-REPAIR study was successful access, deployment, and positioning of the implant and reduction of the septolateral annular diameter at the end of the procedure and at discharge. The primary safety endpoint was the overall rate of major serious adverse events (MSAEs) (a composite endpoint of death, myocardial infarction, cardiac tamponade, device-related cardiac surgery, and stroke) and serious adverse device effects through post-procedural day 30.

An independent clinical event committee (Cardiovascular Research Foundation, New York, New York) collected and adjudicated both the MSAEs and serious adverse device effects.

ECHOCARDIOGRAPHIC ASSESSMENT. All echocardiograms were analyzed at an independent core laboratory (Cardiovascular Research Foundation) that followed the American Society of Echocardiography standards. Transthoracic echocardiograms were performed according to previously published guidelines (21,22). The biplane Simpson's method of discs was used to measure the LVEF. The TR jet was used to estimate the RV systolic pressure via the Bernoulli equation ($4v^2$, where v is the maximum velocity of the TR jet). The right atrial pressure was estimated using the size and collapsibility of the inferior vena cava visualized in the subcostal window. TR was assessed using standard 2-dimensional color Doppler methods. In addition, because of the ellipticity of the regurgitant orifice, the vena contracta width diameters were measured in 2 orthogonal planes (simultaneous multiplane image) or from the 4-chamber view and the inflow view, and averaged to obtain the mean vena contracta width. Quantitation of effective regurgitant orifice area (EROA) and regurgitant volume was also performed by proximal isovelocity surface area (PISA) and Doppler volumetric methods. The tricuspid annulus was measured from the 4-chamber view in end-diastole. Severity of TR was graded according to the 5-grade scheme proposed by Hahn and Zamorano (23).

STATISTICAL ANALYSIS. Continuous variables were descriptively summarized by mean ± SD. All comparisons were based on paired data. A paired Student's *t*-test was used to compare continuous variables between 2 time points. Categorical variables were descriptively summarized with counts and percentages. Wilcoxon signed rank test was used to compare categorical variables between 2 time points. Time-to-event variables were analyzed using Kaplan-Meier survival analysis. An alpha level of 0.05 was used for all 2-sided significance tests. Statistical analyses were performed using SAS Software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Mean patient age was 75.2 ± 6.6 years, and the majority of patients were female (n = 22; 73.3%). Twenty-five patients (83.3%) were in New York Heart Association (NYHA) functional class III to IV, and mean N-terminal pro-B-type natriuretic peptide level was elevated at 2,924.9 ± 3,030.1 pg/ml. Etiology of TR was functional in 30 of

TABLE 2 Changes in Echocardiographic Variables Between Baseline, 30 Days, and 6 Months

Echo TTE	Baseline	30 Days	Change	p Value	Baseline	6 Months	Change	p Value
LV ejection fraction, %	57.2 ± 10.5 (22) (29.5, 71.0)	57.7 ± 8.0 (22) (37.2, 71.0)	0.5 ± 7.9	0.7664	57.1 ± 10.7 (22) (29.5, 71.0)	58.5 ± 7.3 (22) (41.2, 70.7)	1.3 ± 7.8	0.4339
Estimated systolic pulmonary artery pressure, mm Hg	35.8 ± 10.6 (28) (16.0, 59.2)	39.6 ± 10.7 (28) (24.0, 67.3)	3.8 ± 11.8	0.0980	36.1 ± 10.9 (25) (16.0, 59.2)	38.9 ± 7.1 (25) (25.6, 56.0)	2.7 ± 11.2	0.2324
PISA EROA, cm^2	0.79 ± 0.51 (21) (0.18, 1.82)	0.39 ± 0.32 (21) (0.12, 1.42)	−0.40 ± 0.41	0.0003	0.76 ± 0.46 (18) (0.18, 1.70)	0.39 ± 0.25 (18) (0.13, 0.88)	−0.37 ± 0.36	0.0004
Mean vena contracta width, cm	1.26 ± 0.45 (18) (0.55, 2.50)	0.90 ± 0.39 (18) (0.37, 1.65)	−0.36 ± 0.29	<0.0001	1.20 ± 0.43 (21) (0.55, 2.50)	0.88 ± 0.37 (21) (0.35, 1.7)	−0.32 ± 0.28	<0.0001
TR regurgitant volume, ml	79.4 ± 29.6 (7) (45.0, 116.9)	43.7 ± 34.1 (7) (10.3, 110.3)	−35.6 ± 35.3	0.0370	87.4 ± 32.3 (7) (45.0, 145.0)	49.5 ± 31.0 (7) (23.8, 95.0)	−37.9 ± 37.2	0.0357
TV annulus end-diastolic septolateral diameter, 4CH view, mm	42.2 ± 0.5 (18) (31.5, 49.0)	37.8 ± 3.3 (18) (31.0, 42.1)	−4.5 ± 4.3	0.0004	41.6 ± 5.3 (15) (31.5, 49.0)	37.8 ± 3.4 (15) (32.0, 43.0)	−3.8 ± 3.7	0.0014
LV Doppler stroke volume, ml	59.2 ± 19.7 (19) (30.2, 95.3)	64.5 ± 12.1 (19) (42.5, 83.2)	5.2 ± 11.9	0.0716	61.1 ± 17.7 (16) (36.3, 85.9)	64.6 ± 11.7 (16) (46.0, 87.7)	3.5 ± 11.9	0.2561
RV end-diastolic diameter mid-section, cm	3.81 ± 0.62 (26) (2.39, 4.80)	3.74 ± 0.58 (26) (2.60, 4.70)	−0.07 ± 0.51	0.4943	3.76 ± 0.61 (25) (2.39, 4.80)	3.72 ± 0.59 (25) (2.85, 4.70)	−0.04 ± 0.51	0.7051

Values are mean ± SD (n) and (minimum, maximum). Change (mean ± SD) were calculated for paired observations, and p values were calculated by Student's *t*-test for paired observations. TR regurgitant volume was calculated from PISA EROA.

CH = chamber; LV = left ventricular; PISA EROA = proximal isovelocity surface area effective regurgitant orifice area; RV = right ventricular; TR = tricuspid regurgitation; TTE = transthoracic echocardiography; TV = tricuspid valve.

the 30 patients (100%). The most common comorbidities included atrial fibrillation (n = 28; 93.3%), moderate to severe renal impairment (n = 16; 53.3%), and diabetes (n = 8; 26.7%). Mean EuroSCORE II (European System for Cardiac Operative Risk Evaluation) was 4.1%, and STS (Society of Thoracic Surgeons) mortality score was 2.6% (Table 1). Six-month follow-up was performed in 26 patients (3 patients died before their 6-month visit, and 1 missed the visit).

ECHOCARDIOGRAPHIC RESULTS. At baseline, a majority of patients had preserved LVEF (57.5 ± 10.8%). No clinically relevant or untreated left-sided heart valve disease was detected. Systolic pulmonary artery pressure was 35.9 ± 10.5 mm Hg. At baseline, the septolateral diameter was 41.9 ± 4.6 mm, demonstrating tricuspid annular dilatation for the majority of patients. Severe-to-torrential TR defined by PISA EROA was measured in 19 of 25 patients (76%); 5 (20%) presented with moderate TR, and 1 (4%) with mild TR. The severity of TR was assessed by multiple quantitative measurements of parameters such as vena contracta width, PISA, EROA, and regurgitant volume, which were all elevated as shown in Table 2.

After successful implantation and contraction of the tricuspid implant (Table 3), annular dimensions were significantly reduced from 41.6 ± 4.9 mm to 36.2 ± 4.7 mm at discharge. This reduction was stable at 30 days (42.2 ± 5.1 mm to 37.8 ± 3.3 mm; p = 0.0004) and at 6 months (41.6 ± 5.3 mm to 37.8 ± 3.4 mm; p = 0.0014) (Figure 2). As a direct result of the transcatheter annular reduction, TR severity was significantly reduced for all assessed parameters (Table 2, Figure 3). Although 14 of 18 patients (78%) were diagnosed with severe, massive, or torrential TR at baseline by PISA EROA, only 5 patients (28%) presented with severe or greater TR at 6 months (p = 0.0020).

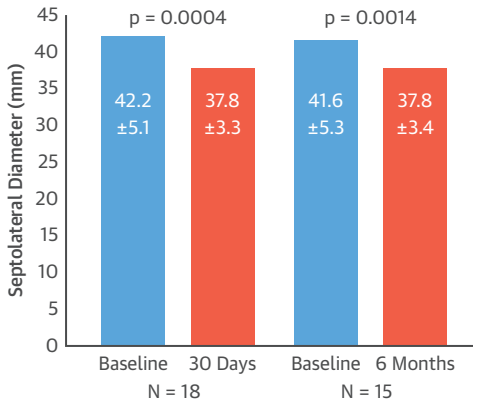
TABLE 3 Procedural Characteristics and Safety Profile (N = 30)

Procedural characteristics	
In-hospital death	1
Length of stay in hospital, days	8.5 ± 5.6
Length of stay in ICU, days	2.0 ± 1.8
Procedure time, min	254.5 ± 92.8
Implant size, mm	
89–96	2
97–104	4
105–112	6
113–120	18
Number of anchors	16 ± 1
Adjudicated 30-day events, n	
Death	2
Stroke	1
Myocardial infarction	0
Bleeding complications*	4
Fatal	1
Life-threatening	1
Extensive	2
Coronary complications	3
Device-related cardiac surgery	0
Renal failure	1
Conduction system disturbance	1
Ventricular arrhythmia	2

Values are n or mean ± SD. Clinical event committee adjudicated. *Mitral Valve Academic Research Consortium criteria guidelines.

ICU = intensive care unit.

FIGURE 2 Septolateral Annular Paired Measurements for the Tricuspid Valve Reconstruction System



Septolateral annular paired measurements at baseline, 30 days, and 6 months for the tricuspid valve reconstruction system. The annular dimension was reduced from 41.6 ± 5.3 mm at baseline to 37.8 ± 3.4 mm at 6 months.

Left ventricular stroke volume, an important determinant of cardiac output, increased from 59.2 ± 19.7 ml to 64.5 ± 12.1 ml (n = 19; p = 0.0716) and 61.1 ± 17.7 ml to 64.6 ± 11.7 ml (n = 16; p = 0.2561) after 30 days and 6 months, respectively (Table 2).

CLINICAL OUTCOMES. The technical success (defined as successful access, deployment, positioning of the implant, and septolateral reduction at intra-procedure and discharge) was 100%. Two patients (6.7%) died within the 30-day periprocedural period, of which 1 death was device related. Within the 6-month follow-up period, 1 additional patient died 151 days after the procedure due to progression of chronic lymphocytic leukemia. At 6 months, the all-cause mortality rate by Kaplan-Meier estimate was 10 ± 5%.

During the periprocedural period, there were no myocardial infarctions or device-related cardiac surgeries (Table 3). During the same period, there was 1 cardiac tamponade (device related) and 1 stroke (not related to the device or procedure). Three subjects experienced 4 protocol-defined MSAEs (MSAE rate 13.3%).

Other clinically important periprocedural reported and adjudicated SAEs were bleeding complications (n = 4), RCA complications (n = 3), ventricular arrhythmias (n = 2), and atrioventricular block (n = 1). The majority of patients (23 of 30; 77%) experienced none of the periprocedural MSAEs or other relevant SAEs events summarized in Table 3. In summary, 4 patients experienced 11 of the 14 events.

One patient experienced an anchor penetration into the RCA during the procedure leading to cardiac tamponade requiring drainage. The vessel injury was treated with balloon angioplasty, and the patient was discharged home in stable condition after a prolonged hospitalization due to recurrent episodes of ventricular tachycardia, which were successfully treated with amiodarone to restore a stable sinus rhythm. Multiple episodes of syncope, which were part of the past medical history, led to subdural bleeding and subarachnoid hemorrhage under oral anticoagulation. The patient died 24 days post-procedure due to cerebral hemorrhage, unrelated to the device or procedure.

One patient experienced an occlusion of an RV branch during the procedure, which was deemed unimportant and left untreated. Post-procedure, the patient experienced recurrent RV cardiac decompensation, acute renal failure requiring dialysis, and respiratory failure post-pneumonia. The patient died 14 days post-procedure due to right heart failure, which was adjudicated as device-related.

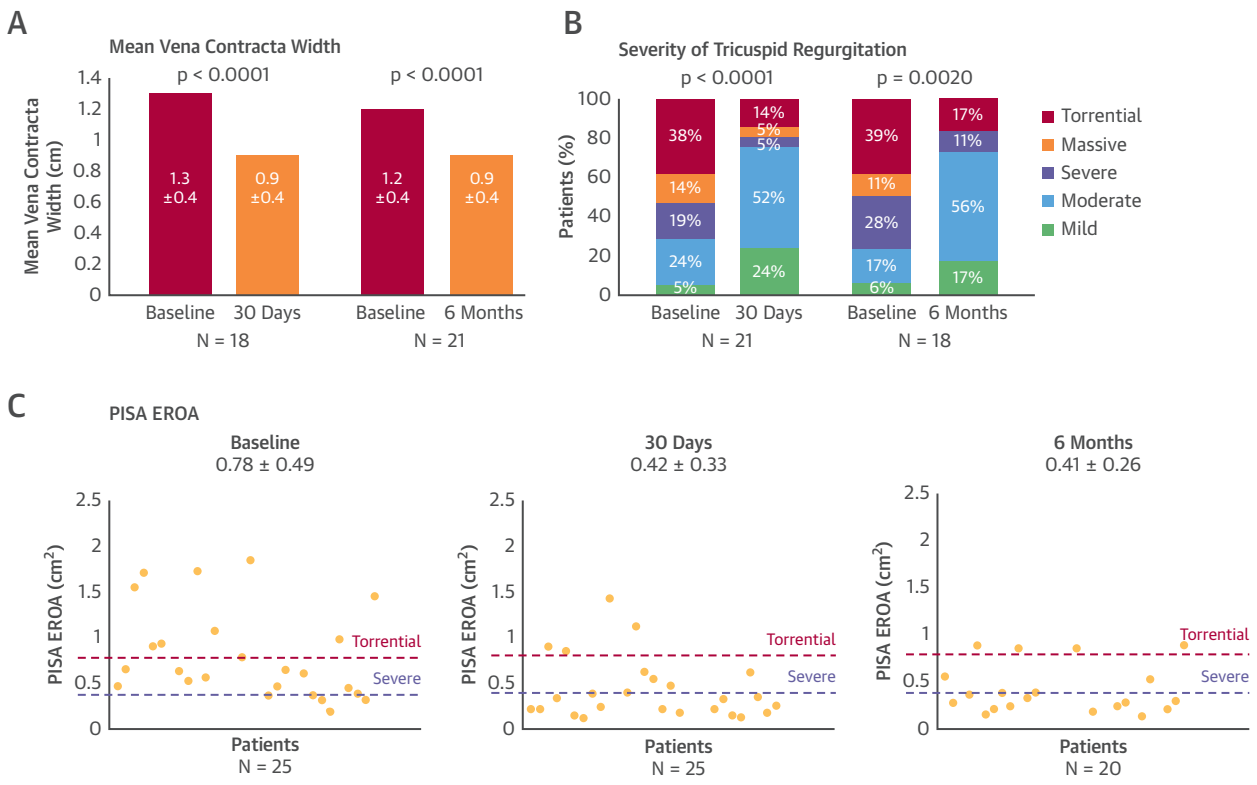
One patient with pre-existing lesions of the distal RCA and of a distal branch experienced worsening of those lesions, and a new lesion developed post-implantation. The lesions were treated by stenting during the procedure. The patient was discharged and exhibited significant clinical improvements at the 6-month follow-up visit.

One patient underwent the index procedure without any complications. One day after discharge, the patient experienced ventricular fibrillation, followed by a complete atrioventricular block the next day, which was treated by a permanent dual-chamber pacemaker. There was no evidence of myocardial infarction.

At 30 days, 20 of 28 patients (71%) improved their functional status, as assessed by NYHA functional class, by 1 or more category. At 6 months, 15 of 25 patients (60%) were in NYHA functional class II and 7 patients (28%) were in NYHA functional class I (p < 0.0001) (Central Illustration, panel A).

The mean 6-min walk distance (6MWD) increased by 60 m, from 266 ± 101 m at baseline to 326 ± 110 m after 6 months (p = 0.0035). The Kansas City Cardiomyopathy Questionnaire (KCCQ) score results improved by 24 points over the 6-month follow-up period, from 46 ± 22 to 70 ± 21 points (p < 0.0001). Edema status was assessed by pitting edema grades (24,25). At baseline, 4 (16%) had an edema grade ++ or worse. At 6 months, no patient had an edema grade ++ or worse, and 18 of 25 patients (72%) had no edema (p = 0.0137). The Central Illustration (panels B to D), illustrate these results for 6MWD, KCCQ, and

FIGURE 3 Echocardiographic Paired Analyses for the Tricuspid Valve Reconstruction System



Echocardiographic paired analyses at baseline, 30 days, and 6 months for the tricuspid valve reconstruction system. **(A)** Mean vena contracta width decreased from 1.2 ± 0.4 cm at baseline to 0.9 ± 0.4 cm at 6 months. **(B)** Extended grades of tricuspid regurgitation severity shows an increase of patients in mild/moderate grades from 29% at baseline to 73% at 6 months. **(C)** Scatter plots of proximal isovelocity surface area effective regurgitant orifice area (PISA EROA) shows a decrease in the number of patients with torrential or severe TR between baseline, 30 days, and 6 months. For continuous variables, the p value was derived from paired Student's *t*-tests to compare baseline to 30 days or baseline to 6 months. For categorical variables, the p values were derived from the Wilcoxon signed rank test to compare baseline to 30 days or baseline to 6 months.

the edema grade results, respectively, at baseline, 30 days, and 6 months.

DISCUSSION

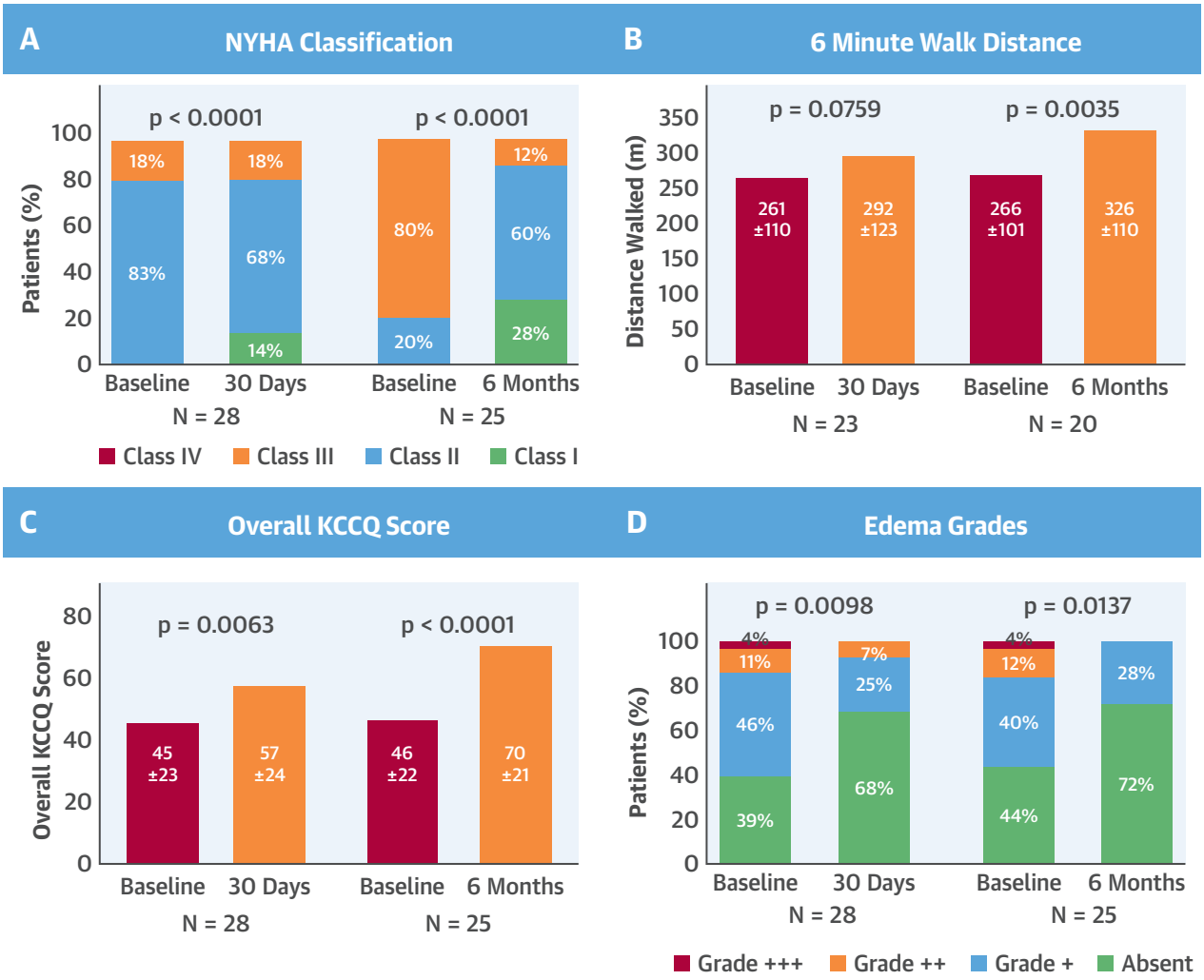
Results from this prospective, multicenter study demonstrate that implantation of a transcatheter tricuspid valve reconstruction system is feasible, safe, and effective in patients with functional TR (Figure 4). The transcatheter tricuspid system used in the tricuspid position is simply a mirror image of the system used in the mitral position. The procedure is performed via transfemoral and venous access without the requirement for transseptal puncture.

The significant reductions in PISA EROA and vena contracta width of 50% and 28%, respectively, at 30 days compare favorably to results reported in the SCOUT (Early Feasibility of the Mitralign Percutaneous Tricuspid Valve Annuloplasty System [PTVAS] Also Known as TriAlign) early feasibility study, which showed a statistically nonsignificant reduction of 22% and 15% in EROA and mean vena contracta width, respectively, at 30 days (26). Circumferential annular reduction with the use of multiple anchors may allow for more significant TR reduction compared with other transcatheter annular repair approaches. The sustained reduction of these parameters with the transcatheter tricuspid system at 6 months are encouraging, and additional studies are warranted.

The device orientation during fluoroscopy is greatly enhanced by placing a visible wire in the RCA, which is in the proximity of the tricuspid annulus and helps to identify the landing zone for the Cardioband anchors. These factors are critical to achieve a high rate of device success (100% in the current study).

Besides fluoroscopy, echocardiography provides essential guidance during the procedure. In order to

CENTRAL ILLUSTRATION **Functional, Clinical, and Echocardiographic Paired Analyses for the Transcatheter Tricuspid Valve Reconstruction System**



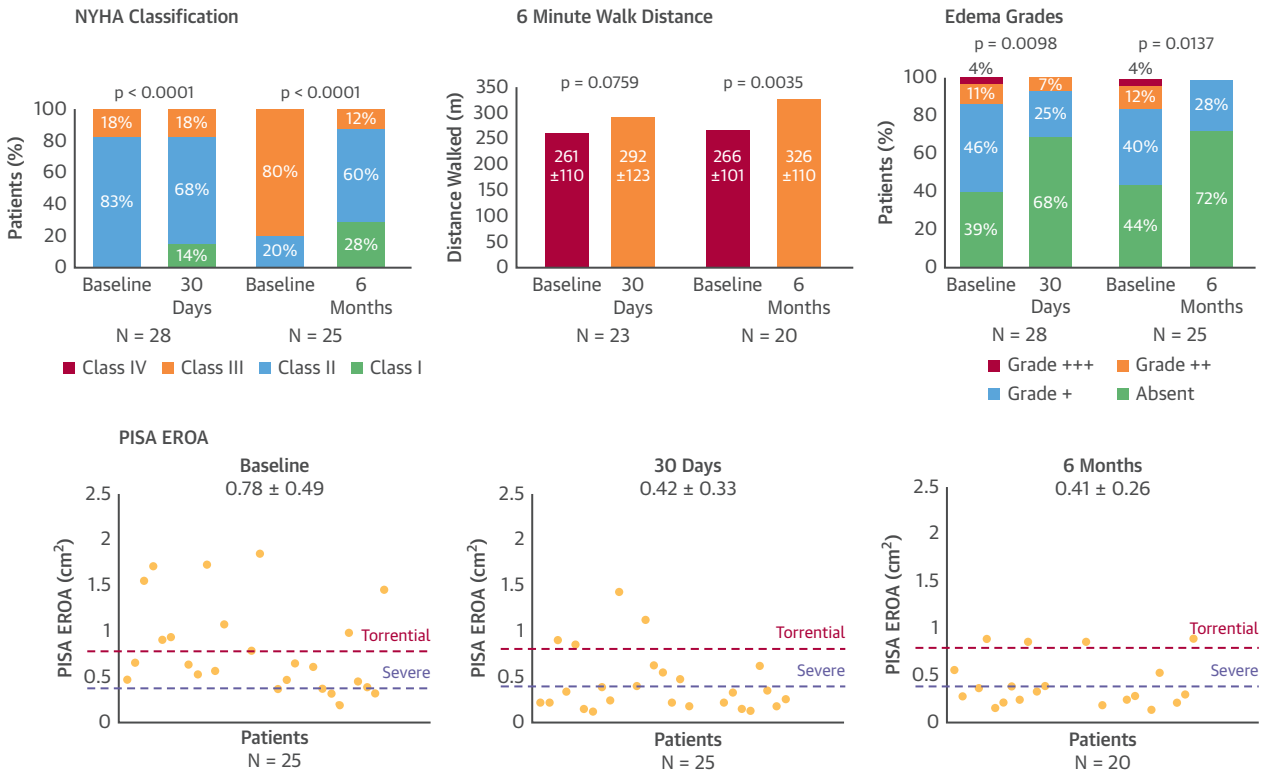
Nickenig, G. et al. J Am Coll Cardiol. 2019;73(15):1905–15.

Functional and clinical paired analyses at baseline, 30 days, and 6 months for the transcatheter tricuspid valve reconstruction system. **(A)** New York Heart Association (NYHA) functional class I/II increased from 20% at baseline to 88% at 6 months; **(B)** 6-min walk distance (6MWD) increased by 60 m, from 266 ± 101 m at baseline to 326 ± 110 m at 6 months; **(C)** Kansas City Cardiomyopathy Questionnaire (KCCQ) score results improved by 24 points over the 6-month follow-up period, from 46 ± 22 to 70 ± 21; **(D)** edema grade ++ or worse, classified by pitted edema grades, decreased from 16% at baseline to 0% at 6 months. For continuous variables, the p values were derived from paired *t*-tests to compare baseline to 30 days or baseline to 6 months. For categorical variables, the p values were derived from the Wilcoxon signed rank test to compare baseline to 30 days or baseline to 6 months.

assure accurate placement of each anchor within the tricuspid annulus, between the leaflet hinge point and the RCA, echocardiographic visualization of the annulus is validated pre-procedurally on the patient in the supine position. In addition, in the future, the use of the latest echocardiography technology including innovative 3-dimensional reconstructive modalities such as multiplanar echocardiography and echocardiography-fluoroscopic fusion may facilitate accurate and timely implantation.

Consequently, patients with poor imaging of the tricuspid valve were excluded from the study. Other patients were excluded for a variety of reasons. Reasons for exclusion in order of frequency included severe tethering (21%), annulus too large for the current device (17%), proximity of pacemaker or

FIGURE 4 The Functional and Clinical Results for the Tricuspid Valve Reconstruction System



The functional and clinical results at baseline, 30 days, and 6 months for the tricuspid valve reconstruction system. New York Heart Association (NYHA) functional class I/II increased from 20% at baseline to 88% at 6 months; 6-min walk distance (6MWD) increased by 60 m, from 266 ± 101 m at baseline to 326 ± 110 m at 6 months; edema grade ++ or worse, classified by pitted edema grades, decreased from 16% at baseline to 0% at 6 months. Scatter plots of proximal isovelocity surface area effective regurgitant orifice area (PISA EROA) shows a decrease in the number of patients with torrential or severe TR between baseline, 30 days, and 6 months. For continuous variables, the p value was derived from paired *t*-tests to compare baseline to 30 days or baseline to 6 months. For categorical variables, the p values were derived from the Wilcoxon signed rank test to compare baseline to 30 days or baseline to 6 months.

defibrillator leads to the leaflets (14%), severe RV dysfunction (14%), mitral valve stenosis and/or regurgitation greater than moderate (9%), and eccentric jet due to pseudo-flail of the tricuspid valve (5%). Other infrequent reasons for exclusions were proximity of the landing zone to the RCA, thin annular anatomy and thick leaflets.

Similar to other feasibility studies, patients treated in the TRI-REPAIR study were pre-selected, and future experience will reveal how widely this procedure can be applied to a broad TR patient population. Patients were enrolled per site-reported echocardiographic parameters. All patients were reported by the sites to have moderate or greater TR having annular diameter >40 mm. The analyses of the patients with implants were later assessed by a core laboratory, where 1 patient was identified as having mild TR and 6 patients were assessed to have annular diameter <40 mm. In a sensitivity analyses removing these 7 patients from the patient cohort, the results do not change the interpretation of the overall findings.

Whereas difficulties in imaging will most certainly be overcome, proximity to the RCA or severe leaflet tethering beyond 10 to 15 mm due to extensive RV dilatation will likely remain important limitations for implantation or any other annular reduction device. Whereas the proximity of RCA poses the risk of anchor penetration increasing the chance of coronary obstruction or pericardial effusion, severe tethering prevents effective TR treatment via annular reduction. In this early experience, we observed 1 anchor penetration into the RCA, 1 occlusion of a side branch, and 1 aggravation of pre-existing stenosis of the distal branches of the RCA. The study provided the valuable learnings that appropriate patient selection and increasing operator experience may help avoid these potentially serious complications.

The promising clinical results of this study are important because there is increasing evidence linking moderate to severe TR to increased morbidity and mortality. Our current knowledge has not unequivocally proven whether TR directly drives poor outcomes or whether TR is only a surrogate of other concomitant disorders such as right- or left-heart failure. This uncertainty and the putative tremendous unmet need increase the urgency to effectively and safely treat TR via novel therapies. Interventions that selectively abolish TR will be able to further our understanding of the prognostic value of TR and of the clinical relevance of its treatment. However, before we embark on comparative powered trials, safety, feasibility, and initial efficacy must be demonstrated with studies such as the TRI-REPAIR study. Because we are in an early stage in the development of transcatheter TR therapies, patients with long-standing disease history and extreme dysfunction of the tricuspid valve are referred to and enrolled in such studies. This is especially true for the current study patient population. Two-thirds of patients (63.3%) enrolled in the TRI-REPAIR study presented initially with severe or greater TR grade. In this patient population, the average annular diameter was 41.9 ± 4.6 mm, and the coaptation defect was 8.1 ± 2.7 mm. Even in these extreme cases, the implantation resulted in a considerable reduction of TR; 14 of 20 patients (70%) presented with moderate or mild TR after 6 months, demonstrating the therapeutic potency of this device. It may be argued that these patients have already been at a late stage of the disease and that long-term benefit may be uncertain. However, despite the inclusion of such patients, the overall results of the study are very promising, showing a significant reduction of all accepted echocardiography parameters defining TR severity. In addition, TR reduction was sustained through the 6-month follow-up, because all quantitative echocardiographic parameters remained stable between 30 days and 6 months. Interestingly, the vena contracta width showed further reduction over time and longer follow-up will determine its correlation to positive RV reverse remodeling following reduction of TR.

In the TRI-REPAIR study, procedure time decreased as operator experience increased, indicating a learning curve that is to be expected for any new device. Furthermore, procedure times were lower for operators with Cardioband mitral system experience, showing a shortened learning curve for those already familiar with the device.

Several other devices are currently under investigation for TR treatment including the edge-to-edge technique, annular repair via paired pledgets, insertion of a spacer in the valve orifice, or valve replacement (11–17,24–27). As of today, data are limited, and no head-to-head comparison is available. However, the potential benefits of the transcatheter tricuspid system may be that it effectively addresses the leading pathophysiology of functional TR, which is annular dilatation. It does not require large vascular or even transatrial access, and it allows for future additional treatment modalities. This may be an especially attractive option in patients with extensive coaptation defects where annular reduction with the system could be combined with leaflet therapy in order to completely abolish TR.

It has been repeatedly shown that even limited reduction of TR is accompanied by a clinical improvement in treated patients (28,29). In the TRI-REPAIR study, TR reduction was substantial. The change in LV stroke volume was clinically significant with an upward trend of 7% at 30 days and 9% at 6 months, from baseline. Consequently, patients significantly benefited functionally and clinically as assessed by improvement in NYHA functional class, edema grade, 6MWD, and KCCQ score.

STUDY LIMITATIONS. This is a feasibility study in a limited patient number with mid-term follow-up time. Due to the nature of the study design and the absence of a gold standard for tricuspid treatment, a control group is missing. Therefore, the presented findings are encouraging and hypothesis-generating and warrant further confirmation.

CONCLUSIONS

The TRI-REPAIR study shows that the transcatheter tricuspid annular reduction system safely and significantly reduces TR through annular reduction, which results in symptom relief and better quality of life. The study provided valuable learnings that will help improve the safety and performance of the device in the future, and sets the stage for further larger-scale trials to explore the potential impact of annular reduction on morbidity and mortality in patients experiencing moderate to severe TR.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The transcatheter tricuspid annular reduction system is the first commercially available transcatheter therapy for treatment of tricuspid valve disease. When employed in patients with moderate to severe tricuspid regurgitation, the system is associated with favorable clinical and functional outcomes at 6 months.

TRANSLATIONAL OUTLOOK: Larger, longer-term studies are needed to confirm these findings and define patients most likely to benefit from this treatment option.

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KEY WORDS annular reduction, tricuspid regurgitation, tricuspid repair, TRI-REPAIR