

Transcatheter Tricuspid Valve Therapies

A look at the current state of this final valve frontier.

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The tricuspid valve has long been described as the “forgotten valve” and for good reason. In the United States, it is estimated that approximately 1.6 million individuals have severe tricuspid regurgitation (TR).¹ Despite a clear association with TR severity and mortality, fewer than 8,000 patients undergo surgical tricuspid repair or replacement. Most patients with severe TR are managed medically with suboptimal therapies, resulting in modest amounts of clinical improvement. A comprehensive assessment of the etiologies of TR can be found in Table 1.²

Patients who do undergo tricuspid valve surgery are typically referred after years of medical therapy and have reached high levels of surgical risk, primarily secondary to deterioration of right ventricle (RV) function, as well as from progression of other comorbidities. Fortunately, there is an increasing number of novel transcatheter treatments for patients with severe TR. Many challenges are faced in this space, including gaining understanding of the unique anatomic challenges, accurate echocardiographic preprocedural and intraoperative assessment, and postprocedure quantification of regurgitant reduction and clinical improvement. In this article, we focus on an understanding of the anatomic considerations that are critical for potential transcatheter therapies and look at the devices that have at least undergone first-in-human study.

ANATOMIC CHALLENGES

Tricuspid valve anatomy is somewhat more complex compared with left-sided valves in that it consists of three leaflets (anterior, posterior, and septal), the chordae tendinae, and usually three papillary muscles.³ The anatomy can be highly variable, with the most characteristic feature of the normal tricuspid valve being the presence of direct attachments of chords from the septal leaflet to the ventricular septum.⁴ The anterior leaflet is the largest, and the septal leaflet is the smallest. The annulus is a complex nonplanar structure with a more

flattened oval shape than the saddle-shaped mitral annulus (Figure 1A). It is also a dynamic structure, changing its shape and size with loading conditions or during the cardiac cycle and has a larger orifice than the mitral valve.

During functional TR, the initial RV dilation leads to tricuspid annulus (TA) dilation. Annular dilation is the dominant mechanism of functional TR.^{5,6} Progressive TA dilation occurs in its anteroposterior plane, corresponding to the free wall of the RV, while septal dilation is limited

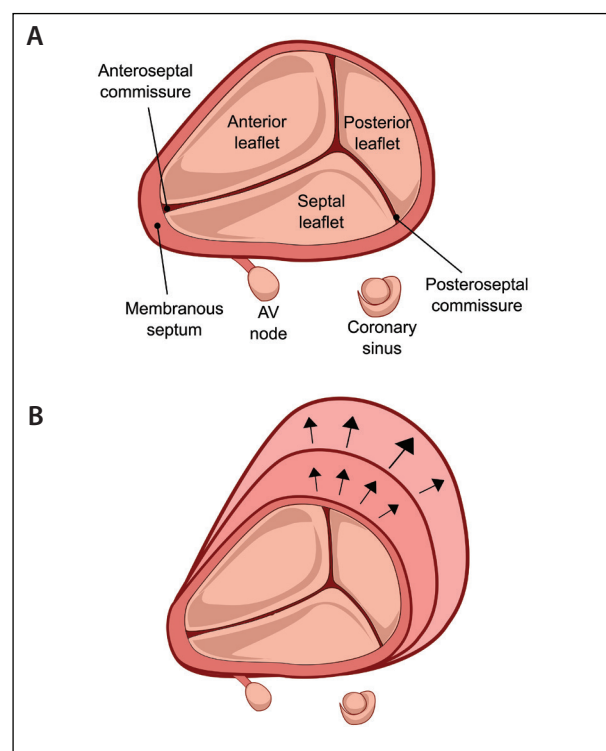


Figure 1. Tricuspid valve anatomy from surgeon's view (A). Impact of progressive annular dilation, primarily on the anterior and posterior annulus, causing worsening TR (B).

TABLE 1. TR ETIOLOGIES

Morphologic Classification (% With Severe TR)	Disease Subgroup	Specific Abnormality
Primary leaflet abnormality (25%)	Congenital	• Ebstein's anomaly
		• Tricuspid valve tethering associated with perimembranous VSD and VSA
		• Other (eg, giant right atrium)
	Acquired disease	• Carcinoid
		• Degenerative (myxomatous)
		• Endocarditis
		• Endomyocardial fibrosis
		• Iatrogenic (pacing leads, RV biopsy)
		• Rheumatic
		• Trauma
		• Other (eg, ischemic papillary muscle rupture)
Secondary, functional (75%)	Left heart disease	• LV dysfunction or valve disease
	Right ventricular dysfunction	• RV cardiomyopathy (eg, ARVD) • RV ischemia • RV volume overload
	Pulmonary hypertension	• Chronic lung disease • Left-to-right shunt • Pulmonary thromboembolism
	Right atrial abnormalities	Atrial fibrillation
Other	Postoperative	Recurrent TR after surgical intervention
Abbreviations: ARVD, arrhythmogenic right ventricular dysplasia; LV, left ventricle; RV, right ventricle; TR, tricuspid regurgitation; VSA, ventricular septal aneurysm; VSD, ventricular septal defect.		

because of its anatomic relation with the fibrous skeleton of the heart (Figure 1B). Significant TR occurs when the anterior and posterior leaflets are pulled away from their coaptation point, resulting in TR jets. Leaflet tethering appears at more advanced stages of RV dilation and papillary muscle displacement.⁶

Several unique anatomic challenges exist for transcatheter treatment of TR and are summarized in the *Anatomic Challenges of Transcatheter Tricuspid Valve Treatment* sidebar. First, the annulus is made of fibrofatty components, which may hinder effective device anchoring.³ Second, the right coronary artery lies in close proximity to the anatomic target for annular reduction, the antero-lateral portion of the valve, which poses a potential risk of iatrogenic coronary damage. Third, the majority of

patients with severe secondary TR have an enlarged TA (≥ 40 mm to > 70 mm) that is nonplanar and lacks calcium, making it difficult to perform transcatheter tricuspid valve replacement. Fourth, the atrioventricular node lies near the septal leaflet, and interaction with the device may lead to conduction disturbances. Fifth, the presence of a preexisting pacemaker or defibrillator leads could also limit the feasibility of a transcatheter technique.³

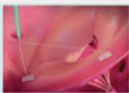
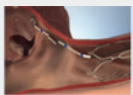
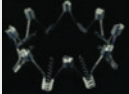
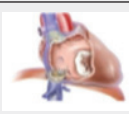
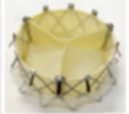
TRANSCATHETER TREATMENT OPTIONS FOR SEVERE TR

The current transcatheter approaches for treating TR can be grouped by mechanism of action, including annuloplasty systems, coaptation devices, leaflet devices, caval valve implantation, and tricuspid valve replacement. All of the devices discussed in the following sections are in the early phases of development in the TR space, and only one has completed an early feasibility trial. Despite this, there is significant excitement regarding the potential benefits of these therapies. For the sake of brevity, we limit our discussion to technologies that have been studied in first-in-man trials. We have done our best to identify the most recent data for each technology that have been published or presented at a major scientific meeting. A summary of these devices can be found in Table 2.

Trialign Percutaneous Tricuspid Valve Annuloplasty System

The Trialign system (Mitralign, Inc.) was originally developed for treatment of functional mitral regurgitation. It is a percutaneous annuloplasty system that is designed to perform a posterior annular plication, mimicking the Kay surgical procedure (ie, converting an incompetent tricuspid valve into a bicuspid valve). A steerable catheter is used to advance a radiofrequency wire through the right internal jugular vein across the annulus, and then pledgets are delivered. Two pledgets are usually placed at the septoposterior and anteroposterior commissure; the two pledgeted sutures are then cinched together using a dedicated plication lock device to produce effective obliteration of the posterior leaflet.⁷ When necessary, a second

TABLE 2. CURRENT TRANSCATHETER THERAPIES FOR TR THAT HAVE UNDERGONE FIRST-IN-HUMAN STUDY

Device Image	Device Name, Mechanism of Action	Number of Patients Treated	Ongoing Studies	Summary
	Trialign, annuloplasty	~60	SCOUT II and CE Mark study	• Good early results with excellent safety profile • Small footprint • 20% device failure at 1 month in SCOUT • Addition of second pair of pledgets should further improve results
	TriCinch, annuloplasty	~25	PREVENT	• Good initial results • Large number of late device pullouts, but the device is being redesigned • Redesign should allow for improved efficacy profile
	Cardioband, annuloplasty	~20	TRI-REPAIR	• True annular device • Good reduction in TR, but limited number of patients reported • Large reduction in orifice may have an impact on the right coronary artery
	Iris, annuloplasty	2 (Sx)	—	• Complete annuloplasty • Only performed surgically to date
	MIA, annuloplasty	2 (Sx)	STTAR	• Only performed surgically to date • Small footprint • Must be translated to transcatheter approach
	Forma, annular spacer	> 40	SPACER	• Has shown significant improvements in quality of life • Difficult to quantify TR after placement • Large footprint
	MitraClip, "leafletplasty"	> 300	—	• Proven technology in mitral space • Readily available at most centers • Does not target annular dilation
	Sapien XT, CAVI	Unknown	HOVER and TRICAVAL	• Ventricularization of the right atrium • Has shown improvement in quality of life
	Gate, valve replacement	2 (1 Sx)	—	• Has the ability to eliminate TR • Can treat a wide range of TR etiologies • Unclear how patients will tolerate the large footprint

Abbreviations: CAVI, caval aortic valve implantation; Sx, surgical approach; TR, tricuspid regurgitation.

pair of pledgets can be implanted on the anterior annulus to optimize the final result.⁸

The early feasibility SCOUT study that included 15 patients showed an acute implantation success of 100%, with one patient requiring right coronary artery stenting.⁹ At 30 days, implantation success was 80% with three single-pledget annular detachments and without reintervention.

A significant reduction in tricuspid annulus, effective regurgitant orifice area (EROA), and left ventricular stroke volume was reported. In the intention-to-treat cohort, there were significant improvements in New York Heart Association (NYHA) functional class ($\geq$ class I; $P = .001$), Minnesota Living With Heart Failure Questionnaire (47.4 ± 17.6 to 20.9 ± 14.8 ; $P < .001$), and 6-minute walk

test ($245.2 \text{ m} \pm 110.1 \text{ m}$ to $298 \text{ m} \pm 107.6 \text{ m}$; $P = .008$). Continued improvement was seen out to 6 months. The performance of the device is currently under investigation in the SCOUT II study, a nonrandomized, open-label clinical study recruiting 30 patients with evidence of functional TR (FTR) secondary to annular dilation. This device has also been described for use in treating pacemaker-induced TR in two patients.¹⁰

TriCinch Tricuspid Valve Repair System

The TriCinch system (4Tech Cardio Ltd.) is a catheter-based device that anchors to the tricuspid annulus to reduce septolateral dimensions while preserving the native anatomy. It is performed via the femoral vein with a steerable delivery system. The device consists of a corkscrew anchor and a nitinol stent delivery system that is connected to the corkscrew using the Dacron band. Tension can be applied while checking the effective reduction of the septolateral diameter of the tricuspid valve on echocardiography. The implantation is completed with the deployment of the stent in the inferior vena cava.

The ongoing PREVENT trial is evaluating patients with severe FTR. Preliminary data report successful procedures in 18 patients (85%), with a significant acute reduction in TR achieved in 94% of patients.^{11,12} However, two procedures were aborted due to hemopericardium, and in four cases, late anchor detachment was reported without any resulting serious adverse events. There is limited follow-up available on these patients, and data on the long-term efficacy of the device in terms of residual TR are needed. The company is currently reconfiguring the anchoring system in the hopes of reducing device pull-out and to increase the overall efficacy of the procedure.

Cardioband Annuloplasty System

The Cardioband system (Edwards Lifesciences) is a direct, surgical-like annuloplasty device originally designed for the mitral valve and inserted through a 24-F sheath placed in the femoral vein. Approximately 16 anchors are implanted in the posterior annulus on the beating heart to fixate the device, which is then cinched. As a result, the annulus diameter is restricted, and the regurgitation diminished. The procedure is performed under fluoroscopic and transesophageal echocardiographic guidance. Preliminary data presented at EuroPCR from the TRI-REPAIR study reported on 20 patients,¹³ and showed that the 30-day mortality rate was 10% (2/20). In seven of the patients, there was a 44% relative reduction in proximal isovelocity surface area EROA ($P < .05$) and a vena contracta relative reduction of 29%, although echocardiographic data from all 20 patients are still awaiting final results from the core lab at this time.

Iris Complete Annuloplasty Ring

The Iris device (Millipede, Inc.) is a repositionable, complete annuloplasty ring that has been used clinically in the mitral and tricuspid positions. Of note, the Iris device does not preclude other future percutaneous options. To date, two patients have undergone tricuspid implantation of the Iris device during concomitant mitral intervention through an open surgical approach, with a tricuspid diameter reduction of 42% to 45% and abolishment of TR in both cases.¹⁴ Moreover, at 6-month follow-up, concomitant reduction of TR and mitral regurgitation prompted positive remodeling of both ventricles. To avoid any possible effects of a complete ring on the native conduction system, the anchor in the region close to the atrioventricular node is not implanted in the annulus and removed.

ANATOMIC CHALLENGES OF TRANSCATHETER TRICUSPID VALVE TREATMENT

- Large tricuspid annulus size
- Nonplanar and elliptical annulus shape
- Fragility of tricuspid annular tissue and narrower annular shelf in comparison to the mitral annulus
- Noncalcified annulus in secondary TR
- Angulation in relation to the superior and inferior vena cava
- Trabeculated right ventricle, muscular bands, and chordae tendinae
- Thin right ventricular free wall
- Proximity of the atrioventricular node and the right bundle of His branch
- Proximity of the right coronary artery to the annulus and risk of coronary injury
- Risk of occluding the coronary sinus, vena cava, or outflow tract
- Large number of patients with pacemaker or defibrillator leads

MIA Device

The MIA minimally invasive annuloplasty device (Micro Interventional Devices, Inc.) is composed of the manufacturer's proprietary low-profile PolyCor anchors and MyoLast implantable elastomer and is designed to reduce annular dimensions and regurgitation after being deployed in the patient's native annulus. The 16-F steerable delivery system has an end deflector that allows deployment of the device in a 270° partial ring pattern. The first two in-human implantations were performed via an open approach and showed a successful acute reduction of tricuspid valve area and no device-related events. The STTAR study will recruit 40 patients to address the feasibility and performance of the MIA device in FTR.

MitraClip System

The MitraClip system (Abbott Vascular) is now an established treatment option for the treatment of both organic and functional mitral regurgitation. Given the ability for off-label use, MitraClip has been the most frequently used device in the tricuspid space. To accommodate approaching the tricuspid valve, most centers have adopted "miskeying" the delivery system in order to achieve an orthogonal orientation. Miskeying is most commonly performed by inserting the delivery system 90° counterclockwise from its typical locking position when used for the mitral valve. Approximately, more than 300 such cases have been performed worldwide.

In a multicenter European registry, 64 patients were treated with MitraClip for TR, and at 9-month follow-up, a significant reduction in TR grade, EROA, regurgitant volume, septolateral diameter, and improved 6-minute walk test results were found for both patients treated for the tricuspid valve alone ($n = 42$) and for those treated in combination with the mitral valve ($n = 22$). Some patients required more than one device due to the complexity of the tricuspid anatomy.¹⁵ The procedure showed favorable safety results including no intraprocedural deaths, cardiac tamponade, emergency surgery, stroke, myocardial infarction, or major vascular complications. Attention should be paid to the high risk of MitraClip entrapment in the subvalvular structures, as well as the significant risk of single leaflet detachment.

Forma Tricuspid Repair System

The Forma system (Edwards Lifesciences) is a spacer that occupies the regurgitant orifice area and provides a platform to enable the coaptation of the native valve leaflets. The device consists of a balloon "spacer" filled with a polycarbonate-urethane foam, and a rail that is anchored at the right ventricle apex using a 20-F sheath introducer. Eighteen patients have currently been treated

for compassionate use, with an 89% implantation success rate, no operative mortality reported, and only one patient who required conversion to surgery due to cardiac tamponade.¹⁶ Fifteen patients completed 1-year follow-up, and there were no deaths and only one hospitalization due to heart failure. Furthermore, clinical end-points at follow-up were encouraging, as most patients reported an improvement in NYHA functional class with an average improvement of 72 meters on a 6-minute walk test and a 17-point improvement on the Kansas City Living With Heart Failure Questionnaire. Finally, at 6-month follow-up, 71.4% of patients had a less than severe TR grade. A multicenter, prospective, early feasibility study and the European/Canadian SPACER trial are currently enrolling 78 patients to test the clinical efficacy of the device.

Caval Aortic Valve Implantation

Caval aortic valve implantation (CAVI) is an alternative approach to directly treating the tricuspid valve by implanting a transcatheter valve in the inferior vena cava, or the inferior vena cava and superior vena cava, with a goal to reduce symptoms of right heart failure by decreasing venous congestion. Concerns have been raised regarding ventricularization of the right atrium, thereby causing further enlargement of the tricuspid annulus. Early experiences have used a balloon-expandable valve normally used to treat aortic stenosis.¹⁷ Two trials, the HOVER¹⁸ and the TRICAVAL, will assess the feasibility of CAVI using the Sapien XT valve (Edwards Lifesciences).

There are also early experiences using a dedicated CAVI device, the Tric Valve device (P&F Products & Features Vertriebs GmbH, in cooperation with Braille Biomedica). Tric Valve is a self-expandable pericardial tissue valve mounted on a nitinol stent frame and inserted through a 20-F expandable sheath using a stiff wire. Compassionate use of the Tric Valve device was successfully performed in four patients for the treatment of severe right ventricular failure. Except for one patient requiring conversion to open surgery due to a suboptimally implanted valve, the others were followed for a mean of 7.4 months and showed improved clinical status. Although predominantly related to noncardiac comorbidities, there was a 75% mortality rate at follow-up.

Gate Tricuspid Valved Stent

In November 2016, the Gate tricuspid atrioventricular valved stent (NaviGate Cardiac Structures Inc.) was successfully implanted in a patient with massive TR. This initial patient underwent implantation via an open right atrial approach. A second case has now been performed via right internal jugular vein access.¹⁹ Early follow-up

results have been encouraging, although the long-term impact of valve replacement on conduction and right ventricular function remains to be seen.

CONCLUSION

Functional TR is a common condition that has a significant impact on patients' functional status and long-term survival. Despite this, surgical treatment for these patients is infrequent and high risk. Although there has been significant "competition" between surgical and transcatheter therapies in the aortic and mitral spaces, the tricuspid valve may represent a unique opportunity for less invasive transcatheter therapies to quickly become the standard of care for all-risk patients. Even though enthusiasm is growing, patients with TR are still undertreated and understudied. Given the lack of guidelines available for treating TR, these patients remain unidentified until the later stages of the disease process. There must be an effort to educate providers to refer patients with TR much earlier in the disease process.

With the excitement of many new technologies entering the space, efforts must be made to standardize evaluation of individual transcatheter therapies. Furthermore, guidelines must be developed to better understand and define the disease process, echocardiographic criteria, and appropriate clinical trial endpoints. The first meeting of an international TR working group took place in June 2017 in the hope of beginning the work that will eventually achieve these goals. Through the efforts of many, hopefully, the tricuspid valve can truly go from forgotten to found. ■

1. Stuge O, Liddicoat J. Emerging opportunities for cardiac surgeons within structural heart disease. *J Thorac Cardiovasc Surg.* 2006;132:1258-1261.
2. Rogers JH, Bolling SF. The tricuspid valve: current perspective and evolving management of tricuspid regurgitation. *Circulation.* 2009;119:2718-2725.
3. Taramasso M, Vanermen H, Maisano F, et al. The growing clinical importance of secondary tricuspid regurgitation. *J Am Coll Cardiol.* 2012;59:703-710.
4. Martinez RM, O'Leary PW, Anderson RH. Anatomy and echocardiography of the normal and abnormal tricuspid valve. *Cardiol Young.* 2006;16(suppl 3):4-11.
5. Frater R. Tricuspid insufficiency. *J Thorac Cardiovasc Surg.* 2001;122:427-429.
6. Dreyfus GD, Martin RP, Chan KMJ, et al. Functional tricuspid regurgitation: a need to revise our understanding. *J Am Coll Cardiol.* 2015;65:2331-2336.
7. Schofer J, Tiburtius C, Hammerstingl C, et al. Transfemoral tricuspid valve repair using a percutaneous mitral valve repair system. *J Am Coll Cardiol.* 2016;67:889-890.
8. Latib A, Mangieri A. Transcatheter tricuspid valve repair: new valve, new opportunities, new challenges. *J Am Coll Cardiol.* 2017;69:1807-1810.
9. Hahn RT, Meduri CU, Davidson CJ, et al. Early feasibility study of a transcatheter tricuspid valve annuloplasty: SCOUT trial 30-day results. *J Am Coll Cardiol.* 2017;69:1795-1806.
10. Meduri CU, Vannan MA, Rajagopal V. First-in-human transcatheter tricuspid annuloplasty in patient with pacemaker lead. Presented at EuroPCR 2017 annual meeting; May 16-19, 2017; Paris, France.
11. Vahanian A. Transcatheter tricuspid valve therapies: 4-Tech description, results and a case. Presented at Transcatheter Cardiovascular Therapeutics 2016 annual meeting; November 1, 2016; Washington, DC.
12. Tchetche D, Denti P, Juliard JM, et al. Innovative transcatheter tricuspid valve repair system. Initial outcomes from the first in human multi-centre study. *J Am Coll Cardiol.* 2016;68:B36.
13. Kuck K. Tricuspid repair with the Edwards Cardioband system: results of the TRI-Repair Study. Presented at EuroPCR 2017 annual meeting; May 16-19, 2017; Paris, France.
14. Rogers J. Transcatheter tricuspid valve therapies S: Millipede. Presented at Transcatheter Cardiovascular Therapeutics 2016 annual meeting; October 29, 2016; Washington, DC.
15. Nickenig G, Kowalski M, Hausleiter J, et al. Transcatheter treatment of severe tricuspid regurgitation with the edge-to-edge MitraClip technique. *Circulation.* 2017;135:1802-1814.
16. Perlman G, Rodes-Cabau J, Webb J. Transcatheter tricuspid repair with a new transcatheter coaptation device for the

treatment of severe tricuspid regurgitation: one-year clinical and echocardiographic results. Presented at EuroPCR 2017 annual meeting; May 16-19, 2017; Paris, France.

17. Lauten A, Ferrari M, Hekmat K, et al. Heterotopic transcatheter tricuspid valve implantation: first-in-man application of a novel approach to tricuspid regurgitation. *Eur Heart J.* 2011;32:1207-1213.

18. O'Neill BP, Wheatley G, Bashir R, et al. Study design and rationale of the heterotopic implantation of the Edwards-Sapien XT transcatheter valve in the inferior vena cava for the treatment of severe tricuspid regurgitation (HOVER) trial. *Catheter Cardiovasc Interv.* 2016;88:287-293.

19. Navia J, Kapadia S, Svensson L. First-in-man experience of a novel transcatheter tricuspid valve replacement in patient with severe tricuspid valve regurgitation. Presented at EuroPCR 2017 annual meeting; May 16-19, 2017; Paris, France.

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