Emerging Transcatheter Options for Tricuspid Regurgitation

Ankur Kalra, M.D.[a-c]; *Angad S. Uberoi,* M.D.[a]; *Azeem Latib,* M.D.[d]; *Sahil Khera,* M.D.[e]; *Stephen H. Little,* M.D.[a,b]; *Deepak L. Bhatt,* M.D., M.P.H.[f]; *Michael J. Reardon,* M.D.[a,b]; *Neal S. Kleiman,* M.D.[a,b]; *Colin M. Barker,* M.D.[a,b]

[a]HOUSTON METHODIST DEBAKEY HEART & VASCULAR CENTER, HOUSTON METHODIST HOSPITAL, HOUSTON, TEXAS; [b]WEILL CORNELL MEDICAL COLLEGE, NEW YORK, NEW YORK; [c]UNIVERSITY HOSPITALS CLEVELAND MEDICAL CENTER, CASE WESTERN RESERVE UNIVERSITY, CLEVELAND, OHIO; [d]EMO-GVM CENTRO CUORE COLUMBUS AND SAN RAFFAELE SCIENTIFIC INSTITUTE, MILAN, ITALY; [e]MASSACHUSETTS GENERAL HOSPITAL, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS; [f]BRIGHAM AND WOMEN'S HEART & VASCULAR CENTER, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

ABSTRACT: Tricuspid regurgitation (TR) presents as either primary valve pathology or secondary to pulmonary or left-sided heart disease. Severe TR portends a worse prognosis independent of age, right ventricular size and function, severe left ventricular dysfunction, and increased pulmonary arterial pressures. Surgical treatment for TR has mostly been limited to patients undergoing mitral valve repair since those at high surgical risk are not candidates for traditional TR surgery. For these patients, minimally invasive techniques could be of great benefit, yet these techniques have been slow to develop because of the various anatomic and physiological aspects of the tricuspid valve apparatus. Several promising new techniques are currently undergoing clinical investigation, including caval valve implantation, percutaneous tricuspid annuloplasty techniques (Trialign, TriCinch, Cardioband), edge-to-edge repair with the MitraClip system, the FORMA device, and the GATE tricuspid Atrioventricular Valved Stent. Further evaluation of their safety and long-term efficacy is warranted prior to commercial approval and widespread adoption.

INTRODUCTION

Although the tricuspid valve is often called the "forgotten valve," its pathology is an important cause of morbidity and mortality. The most common tricuspid valve pathology encountered in cardiovascular diseases is tricuspid regurgitation (TR). TR may occur due to primary valve pathology (including congenital TR, infective endocarditis, prolapse, and rheumatic heart disease), but it is more common secondary to pulmonary disease, left ventricular (LV) dysfunction, aortic or mitral valve disease leading to raised pulmonary arterial pressures, right ventricular pressure and/or volume overload, and subsequent tricuspid annular dilation. Other etiologies include iatrogenic TR due to pacemaker or defibrillator lead placement or following right ventricular (RV) endomyocardial biopsy. Severe TR heralds a worse prognosis independent of the severity of LV dysfunction, pulmonary hypertension, RV size and function, or age.[1]

Although the impact of severe TR on morbidity and mortality is well known, treatment options have lagged behind, especially for patients with multiple comorbidities and high peri- and postoperative risk. In the most common subset of functional TR associated with left-sided heart disease, surgical repair is usually done alongside treatment of mitral valve disease, with contemporary techniques showing low relapse rates.[2] However, there is also a substantial patient population in whom mild TR increases in severity following surgery, and repeat open heart surgery in these cases is associated with very high mortality (10-20%).[3] This, coupled with the failure of medical therapy to improve symptoms and prevent mortality in TR patients with prohibitive surgical risk, highlights an unmet need for a novel, minimally invasive transcatheter treatment to correct tricuspid valve insufficiency.

ANATOMIC CHALLENGES

One of the main obstacles precluding a viable transcatheter treatment option for TR is the complexity of the valve's anatomy. The tricuspid valve apparatus consists of the three valve leaflets arranged in order of decreasing size: anterior, posterior, and septal. These are attached via the chordae tendinae to the papillary muscles, which are much more variable in their anatomy compared to the LV papillary muscles. The tricuspid annulus contributes to the increased complexity of the tricuspid valve apparatus due to its shape and multiplanar, dynamic structure.[4,5] The highest point of the annulus is located at the anteroseptal commissure, and the lowest point is at the posteroseptal commissure, with the anteroposterior commissure lying in between.[4] Unlike the saddle-shaped mitral annulus, the tricuspid annulus has a flattened oval shape.[6] Its shape is dynamic, with changes seen in the tricuspid annular area and perimeter during each cardiac cycle.[4] It has also been noted that the tricuspid annulus assumes a more planar, circular configuration in functional to compared to healthy controls.[5]

Rodés-Cabau and colleagues have summarized the major challenges in developing transcatheter treatment strategies for the tricuspid valve.[7] These include (1) large tricuspid annulus size; (2) nonplanar, elliptical annulus shape; (3) fragility of tricuspid annular tissue and narrower annular shelf compared with the mitral annulus; (4) noncalcified annulus in secondary TR; (5) angulation in relation to superior and inferior vena cava; (6) trabeculated RV, muscular bands, and chordae tendinae; (7) thin RV free wall; (8) proximity of atrioventricular node and right His bundle branch; (9) proximity of the right coronary artery to the tricuspid annulus and risk of coronary injury; (10) risk of coronary sinus, vena cava, or outflow tract occlusion; (11) slow flow in the RV; and (12) patients with pacemaker or defibrillator leads.[7]

PHYSIOLOGICAL CHALLENGES

A major physiological challenge in developing effective transcatheter valves is the durability of the prosthetic valve material. Another challenge is quantifying improvement following intervention and meticulously defining the end points of trials testing the procedure's efficacy. For these procedures to gain wider acceptance, there is a need for standardized indicators that not only measure the severity of TR but also quantify both symptomatic relief and reduction in rehospitalization. Standardized data on these parameters will be crucial in allowing interventional strategies to become standard of care for these patients. In addition, tricuspid valve and RV imaging strategies, including transthoracic, transesophageal, and intracardiac echocardiography as well as fusion imaging, must be standardized and modified for this purpose.

Most patients with TR have multiple cardiac and noncardiac confounders for morbidity and mortality. The presence of LV dysfunction, mitral valve pathology, and pulmonary hypertension make it difficult to determine the overall impact of residual TR on a patient's clinical status.

NOVEL TREATMENT STRATEGIES (TABLE 1)

Heterotopic Caval Valve Implantation

Heterotopic caval valve implantation (CAVI) has been suggested for patients whose severe TR (1) causes caval regurgitation and dilation, (2) manifests as peripheral edema, ascites, and congestive hepatopathy refractory to medical treatment, and (3) puts them at prohibitive risk for perioperative mortality. While this technique does not correct the underlying lesion, it produces symptomatic relief and prevents deleterious effects of venous congestion on the liver and peripheral vasculature. Two approaches have been described for valve implantation. One uses a balloon-expandable valve, which requires a landing zone to be placed with a self-expanding stent at the cavoatrial junction before valve deployment.[8] In this approach, the Edwards SAPIEN XT or SAPIEN 3 valve (Edwards Lifesciences), a transcatheter valve used in the treatment of aortic stenosis, is deployed inside the self-expanding stent. The other approach uses a self-expandable device specifically designed for CAVI that can accommodate larger caval sizes, thus preventing the need to pre-stent the caval veins.[9]

Both approaches have thus far been used only in compassionate-use cases—those severely symptomatic patients unable to undergo surgery. Thus, clinical data on outcomes is limited, although these cases establish feasibility of use.[8,9] Data on efficacy, safety, and benefit are needed from large-scale clinical trials with longer follow-up periods. One such trial is HOVER (Heterotopic Implantation Of the Edwards-Sapien XT Transcatheter Valve in the Inferior VEna Cava for the Treatment of Severe Tricuspid Regurgitation), a prospective single-center registry currently underway at Temple University in Philadelphia.[10]

Although CAVI is a novel approach, its use is fraught with issues. First, its applicability is limited to a subset of patients with TR who have progressed to the stage where caval dilation and regurgitation have occurred. This is uncommon, however, as most patients seen in clinical practice have normal caval diameters because the right atrium acts as a reservoir and prevents the regurgitant jet from affecting the venous system. Only in chronic cases does the right atrium become overwhelmed trying to accommodate the regurgitant blood flow, thus necessitating the need for CAVI. Second, the degree of dilation and the diameter of the caval wall have marked variability between patients, necessitating patient-specific device customization. Finally, the proximity of the hepatic vein ostia to the right atrium is yet another important anatomic consideration that may complicate valve deployment in the vena cava.

While CAVI addresses the peripheral venous consequences of TR, it does not treat the valvular regurgitation itself. The right atrial pressures remain elevated, and there is a possibility of adverse events due to ventricularization of the right atrial pressures (e.g., atrial fibrillation and right ventricular volume overload). The incidence of these adverse events must be documented in trials that allow longer follow-up periods. Additionally, more data are needed on whether valve implantation in the superior vena cava is warranted.

Percutaneous Tricuspid Annuloplasty Trialign

Secondary/functional tricuspid regurgitation usually results from tricuspid annular dilation. The Trialign device (Mitralign, Inc.) seeks to reduce the size of the tricuspid annulus by plication

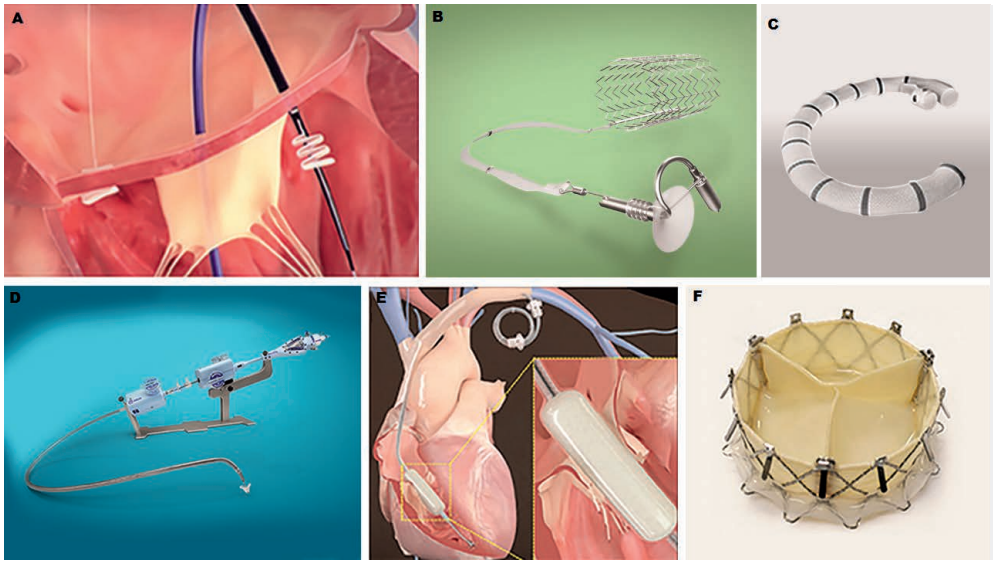

Figure 1.
Emerging transcatheter technologies for tricuspid regurgitation. (A) Trialign device (Mitralign, Inc.). (B) TriCinch system (4Tech Cardio). (C) Cardioband (ValtechCardio). (D) MitraClip system (Abbott Vascular). (E) FORMA tricuspid repair system (Edwards Lifesciences). (F) GATE tricuspid Atrioventricular Valved Stent (NaviGate Cardiac Structures Inc.).

of the muscular (anterior and posterior) part of the annulus, mimicking the Kay bicuspidization procedure of tricuspid annuloplasty (Figure 1 A).[11]

Schofer et al. reported the first-in-man transcatheter tricuspid valve repair using the Trialign system.[12] The procedure was performed on an 89-year-old patient with recurrent right heart failure due to severe isolated TR that was unresponsive to optimal medical therapy. Using transjugular venous access, an 8Fr deflectable wire delivery catheter was passed through the tricuspid valve in a retrograde fashion and was used to place radiofrequency wires in the tricuspid annulus at the anteroposterior and posteroseptal commissures. This was performed under fluoroscopic and transesophageal echocardiography (TEE) guidance to avoid injury to the right coronary artery near the annulus. Using the wires, pledget delivery catheters were passed through the annulus, with pledgeted sutures introduced and cinched on both the atrial and ventricular subannular surfaces. A dedicated plication lock device was then used to bring the two pledgeted sutures together to plicate the annulus, thus reducing the tricuspid annular dimensions. The procedure resulted in a 57% reduction in annular area and a 53% reduction in effective regurgitant orifice area (EROA) as measured by 3-dimensional TEE.[12] It also resulted in improved hemodynamic status, with an increase in stroke volume from 42 mL before the procedure to 72 mL following the procedure, and a decrease in right atrial pressure from 22 mm Hg at baseline to 9 mm Hg.[12] The patient had an uneventful postprocedural course and reported subjective improvement in symptoms.[12]

Since the first report, more than 30 patients have been treated with this device worldwide, with successful pledgeted suture deployment in > 90% of cases.[7] The 30-day data of the completed SCOUT-I study (Early Feasibility of the Mitralign Percutaneous Tricuspid Valve Annuloplasty System [PTVAS] Also Known as Trialign) that were presented at the Transcatheter Cardiovascular Therapeutics (TCT) 2016 annual scientific sessions showed the absence of any major adverse effect in all patients (n = 15).[13,14] There was a significant decrease in tricuspid valve annular diameter from 4.0 ± 0.5 cm to 3.8 ± 0.6 cm ($P = .038$), tricuspid valve annulus area from 12.3 ± 3.1 cm^2 to 11.3 ± 2.7 cm^2 ($P = .019$), proximal isovelocity surface area (PISA) EROA from 0.51 ± 0.2 cm^2 to 0.32 ± 0.2 cm^2 ($P = .036$), and quantitative EROA from 0.9 ± 0.2 cm^2 to 0.6 ± 0.3 cm^2 ($P = .045$). Left ventricular outflow tract stroke volume had a significant increase from 63.6 ± 17.9 mL at baseline to 71.5 ± 25.7 mL at 30 days ($P = .021$). A concomitant improvement in clinical status was also described, with a 22% increase in 6-minute walk test distance ($P = .008$) and reduction in New York Heart Association (NYHA) class from 66.7% NYHA III and 33.3% NYHA II to 53.3% NYHA II and 46.7% NYHA I, respectively ($P = .001$).[14]

TriCinch. The TriCinch system (4Tech Cardio) is another transcatheter tricuspid annuloplasty system being evaluated for use in secondary TR (Figure 1 B). It consists of a corkscrew anchor fixed into the tricuspid annulus near the anteroposterior commissure. The anchor is connected with a Dacron band to a self-expanding nitinol stent. Once the corkscrew is in place in the annulus, tension is applied to the system; this decreases both the dimensions of the tricuspid annulus and the degree of TR. Tension is maintained by deploying the nitinol stent in a subhepatic position in the inferior vena cava. The first-in-man use of this system was

Heterotopic caval valve implantation	Balloon-expandable valves: SAPIEN 3 Self-expandable devices: TricValve
Percutaneous tricuspid annuloplasty	Trialign TriCinch Cardioband Millipede IRIS
Leaflet edge-to-edge repair	MitraClip FORMA Repair System
Atrioventricular valved stent	GATE atrioventricular valved stent

Table 1.
Emerging transcatheter technologies for tricuspid regurgitation.

reported by Latib et al. in 2015, and its safety and efficacy are currently being evaluated in the PREVENT study (Percutaneous Treatment of Tricuspid Valve Regurgitation with the TriCinch System).[15,16]

Cardioband Tricuspid

Cardioband (Valtech) is a percutaneous transcatheter annuloplasty system consisting of an adjustable Dacron band (Figure 1 C), and it is intended to mimic the surgical gold standard. Its first-in-man use in a patient with TR led to a decrease in severity of TR from severe to mild, with a corresponding decrease in regurgitant volume from 264 mL/s to 36 mL/s (by 2-dimensional PISA method).[17] Data on Cardioband's safety and feasibility of use for mitral regurgitation were presented at TCT 2016 annual scientific sessions.

Millipede IRIS. The Millipede IRIS (Millipede Inc.) is a semi-rigid ring device that has been used for both mitral and tricuspid regurgitation. Data on its use in nine surgical patients were reported at the EuroPCR 2016 annual scientific sessions and demonstrated the safety and feasibility of this system. The delivery system for the transcatheter use of this ring is currently under development.

MitraClip Clip Delivery System

While the Trialign and TriCinch systems can be used prospectively in cases of secondary or functional TR, they are not applicable for use in patients with TR due to primary valve disease or mixed etiologies. In these patients, the MitraClip system (Abbott Vascular) is a possible intervention to perform edge-to-edge repair (Figure 1 D). Hammerstingl et al. reported a three-case series in which they performed transcatheter edge-to-edge repair using the MitraClip system via the transjugular route in patients with severe symptomatic TR who were denied surgery due to high surgical risk.[18] The procedures were performed with guidance from fluoroscopy and 2- and 3-dimensional TEE. The clips were introduced into the right atrium, oriented toward the tricuspid commissures, and attached to the leaflet margins guided by predefined echocardiographic views. After placement of each clip, the effect on the severity of TR was assessed in real time, and the procedural steps were repeated if the effect was deemed to be insufficient. All three patients tolerated the procedure well and had uneventful postoperative recovery. On assessment, there was an acute reduction of TR in all patients, measured by decreases in EROA (0.4 ± 0.4 cm^2), inferior vena cava width (3.5 ± 2.1 mm), and tricuspid annulus diameter (14.3 ± 8.9 mm). All patients reported stable clinical status 30 days after the procedure. Braun et al. used this procedure in 18 patients with TR and showed a reduction in the presence of TR grade ≥ 3 from 94% (17 patients) before the procedure to 33% (6 patients) at 30 days post procedure ($P < .001$); in addition, 89% (16 patients) had an improvement of NYHA class.[19] Since then, more than 250 tricuspid MitraClip procedures have been performed worldwide using the transfemoral approach as well as the transjugular approach described above.[20-22]

The MitraClip system has some advantages over percutaneous tricuspid annuloplasty techniques. First, it can be used in primary, secondary, or mixed etiology cases regardless of the cause of TR. Second, interventional cardiologists have gained experience working with the MitraClip system for mitral valve disease, thus flattening its learning curve. The limitations of using MitraClip in TR cases include large coaptation gaps, interference with pacemaker leads, difficulties in imaging grasping of the leaflets, and the need for multiple clips. Although reports are encouraging, more detailed evaluations of the efficacy, technique, and outcomes of this procedure are warranted with larger-scale clinical trials. The possibility of combining this procedure with percutaneous tricuspid annuloplasty techniques, such as the Mitralign system in cases with tricuspid annular dilation,

also needs to be evaluated. In addition, there is controversy about which leaflets should be clipped.

FORMA Repair System

The FORMA tricuspid repair system (Edwards Lifesciences) is another potential option for transcatheter treatment of TR (Figure 1 E). This system is being evaluated for use in patients with TR due to annular dilation and lack of leaflet coaptation. The FORMA system provides a platform for leaflet coaptation called the "spacer," which is placed at the tricuspid orifice and anchored with rails at the RV apex and proximally in the subclavian region. Using fluoroscopic guidance, the spacer is placed via the transvenous route and its position checked with the help of 2- and 3-dimensional TEE. Early results of this device are promising, with all patients showing improved clinical status and decreased TR severity at 30 days.[23] Data from large-scale early feasibility studies are currently awaited.

GATE Tricuspid Atrioventricular Valved Stent

The GATE tricuspid atrioventricular valved stent (NaviGate Cardiac Structures, Inc.) is a novel valved stent that can capture the enlarged annulus in functional TR (Figure 1 F). In its first-in-man use, the device was placed via the transcatheter route in a 64-year-old female patient with severe TR.[24] The valve demonstrated good function postimplantation, and the patient was reported to be clinically stable at 30 days. Currently, more data on the use of this device are awaited.

CONCLUSION

In our march toward developing effective minimally invasive interventional strategies for valvular heart disease, TR is the next frontier requiring the attention and efforts of structural heart teams. Newer devices and systems have shown promise in sporadic reports, and the time is ripe for coordinated large-scale studies to establish the safety, efficacy, and long-term effects of these novel interventions.

KEY POINTS

- Tricuspid regurgitation is an important cause of morbidity and mortality in cardiovascular patients, and there is an unmet need for minimally invasive treatment strategies in patients who are not surgical candidates.
- Various anatomical and physiological aspects of the tricuspid valve apparatus and the right ventricle have precluded the development of these treatment strategies.
- Newer techniques being evaluated include caval valve implantation, percutaneous tricuspid annuloplasty techniques (Trialign, TriCinch, Cardioband), edge-to-edge repair with the MitraClip system, the FORMA device, and the GATE tricuspid atrioventricular valved stent.
- Further evaluation of the safety and long-term efficacy of these techniques is warranted prior to commercial approval and widespread adoption.

Conflict of Interest Disclosure:
Dr. Deepak Bhatt is on the advisory boards of Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences and serves on the board of directors for Boston VA Research Institute and the Society of Cardiovascular Patient Care. He has received honoraria from his roles at the American College of Cardiology, Belvoir Publications, Duke Clinical Research Institute, Harvard Clinical Research Institute, HMP Communications, Population Health Research Institute, Slack Publications, Society of Cardiovascular Patient Care, and WebMD. He also receives research funding from Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, and The Medicines Company as well as royalties from Elsevier. Finally, he is a site coinvestigator for Biotronik, Boston Scientific, and St. Jude Medical and a trustee of the American College of Cardiology.

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