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REVIEW
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Transcatheter interventions for severe tricuspid regurgitation: a literature review

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ABSTRACT The prevalence of tricuspid regurgitation (TR) increases with age, affecting 65%-85% of adults. Primary TR is caused by a congenital or acquired abnormality of the tricuspid valve apparatus (leaflets, chordae, papillary muscles, or annulus). Secondary TR is due to insufficient coaptation from dilation of tricuspid valve annulus due to the right ventricle (RV) or right atrium (RA) remodeling and increased RV pressures. Isolated TR is without increased RV pressures and is associated with atrial fibrillation. Mild TR is a benign disease. Moderate to severe tricuspid regurgitation has independently been associated with increased mortality. Most of these patients are treated medically due to poor outcomes with surgical repair of isolated TR. The in-hospital mortality rate is 8.8%, and the median length of stay in hospital is 11 days resulting in higher healthcare costs. Even if the patients undergo surgical repair or replacement, available data do not show improvement in survival. With a more detailed understanding of the complex anatomy and physiology of the tricuspid valve and significant complications from untreated tricuspid valve disease, the approach to the management of TR has shifted from a conservative approach to a process of prevention and intervention. In the past decade, transcatheter tricuspid valve interventions and tricuspid annuloplasty rings have been developed, contributing to decreased mortality from surgical repair. Transcatheter tricuspid valve intervention techniques have improved survival, quality of life, and reduced heart failure rehospitalization. This review summarizes normal anatomy, types of TR, etiology and different mechanisms of TR, echocardiographic assessment of the severe TR, and highlights various percutaneous transcatheter techniques for tricuspid valve repair.

Compared with other cardiac valves, the tricuspid valve (TV) has received less attention and relatively lower surgical interventions.[1] Tricuspid regurgitation (TR), also known as tricuspid insufficiency, is the most common tricuspid valve disease. It is a condition where the valve between the right atrium (RA) and right ventricle (RV) fails to close correctly. The malfunctioning valve results in the backflow of blood from the right ventricle to the right atrium during systole.

The annual incidence of TR is about 200,000 patients in the US and more than 300,000 patients in Europe. In the US, the prevalence of moderate to severe TR is close to 1.6 million, out of which less than 8000 patients per year undergo surgical repair or replacement of TV.[2,3] TR is predominantly attributed to functional or secondary causes than organic or primary causes of TR. However, emerging evidence from recent trials on right-sided transvenous devices such as pacemakers and implantable defibrillators indicate an increasing role of organic causes in the pathophysiology of primary TR. Clinical assessment of the severity of TR is often challenging due to the lack of clinical features in the early stages. Mild and moderate TR is often managed medically unless there is an indication for repairing the left-sided valvular heart disease. Surgical repair or replacement of the valve is essential to improve symptoms, quality of life and decrease complications in patients with severe TR. Severe TR is also associated with increased mortality independent of left ventricular ejection fraction or pulmonary artery systolic pressure. Moreover, TV procedures are performed with left-sided heart procedures. Severe TR was believed to improve after surgical repair of the mitral or aortic valves. TR affected survival, functional class, and

perioperative outcomes if left untreated while performing left-sided heart surgery.[4]

Isolated TV surgeries are uncommon and associated with high in-hospital mortality rates predominantly due to late surgeries when the RV is irreversibly dilated and dysfunctional.[2,5] There is also an increased risk of residual or recurrent TR after surgical repair of the tricuspid valve.[6] This necessitates the need for less-invasive novel transcatheter techniques to manage severe TR in high surgical risk patients.

ANATOMICAL CONSIDERATIONS

Understanding the anatomy of the tricuspid valve and its relation to neighboring structures is key before performing transcatheter tricuspid interventions effectively and safely. The tricuspid valve is the largest of the four heart valves, and it separates the right atrium from the right ventricle. It is semilunar in shape as the right ventricle is wrapped around the left ventricle. It is constituted by the fibrous annulus, three leaflets, two papillary muscles, and chordae tendineae. Three leaflets (anterior, septal, and posterior) are separated by three commissures: anteroseptal, posteroseptal, and anteroposterior. The anterior is the largest among the leaflets, and the septal is the smallest. The anterior papillary muscle provides chordae attachment to anterior and posterior leaflets, while the medial papillary muscle provides chordae attachment to the posterior and septal leaflets.[7] The tricuspid annulus changes shape during various phases of the cardiac cycle.[8] It has an increased tendency to dilate with ventricular enlargement as it is less stiff and has the largest cardiac valve. It becomes planar and circular with right ventricular dilation, which stretches anterior and posterior portions, but the septal portion of TA remains fixed and unchanged.[9] An atrioventricular node that lies within Koch's triangle is located in close proximity to TV. The triangle of Koch and blood supply to the conduction system must be avoided during TV repair or replacement.[7] Replacement of the tricuspid valve carries a greater risk of damage to the conduction system than a repair.[8]

TYPES OF TR AND ETIOLOGY

Primary TR can be due to congenital or acquired causes. Ebstein's anomaly is the most common congenital cause. Acquired causes include tumors such as carcinoid disease or myxoma, iatrogenic injury such as RV endomyocardial biopsy, transvenous pacing or defibrillator leads, drug-induced leaflet damage such as anorectic drugs, dopamine agonists, and ergot alkaloids, systemic diseases such as systemic lupus erythematosus (SLE) and sarcoidosis, radiation therapy, rheumatic disease, endocarditis, trauma.[7,8,10] Transvenous pacemaker and defibrillator lead-induced TR are the most frequently acquired etiologies of the TR.[10]

Secondary TR is more common than primary TR. It is secondary to the disease process altering RV size and function, resulting in tricuspid annulus dilation followed by leaflet mal-coaptation and ultimately leading to tethering of leaflets. The most frequent causes of secondary TR are left-sided valvular and myocardial disease associated with increased left atrial pressures, pulmonary hypertension, and increased RV afterload. Approximately 50% of patients with severe mitral regurgitation (MR) and more than 25% of patients with severe aortic stenosis (AS) have concomitant moderate and severe TR.[4] Patients undergoing surgery for aortic or mitral valve disease can develop worsening TR, which is associated with decreased survival.[11] In acute or chronic congestive heart failure patients with reduced ejection fraction, significant TR is commonly observed, which can progress further despite optimal medical therapy and cardiac resynchronization therapy. Pulmonary hypertension from causes other than left-sided heart diseases such as primary pulmonary hypertension, pulmonary embolism, and chronic pulmonary disease can cause TR due to increased RV afterload, RV dilation, and dysfunction. Conditions directly affecting RV function, such as inferior wall myocardial ischemia or arrhythmogenic RV dysplasia/cardiomyopathy, can cause TR through the apical displacement of papillary muscles and increased tethering of the TV leaflets.

Isolated TR is mainly present in elderly patients with a high prevalence of atrial fibrillation causing RA dilation, TV annulus dilation, TV leaflets mal-coaptation without right ventricular remodeling in the absence of concomitant pulmonary hypertension or coexisting left-sided heart disease.

ECHOCARDIOGRAPHIC ASSESSMENT

Advanced imaging modalities are helpful in the assessment of TV morphology, mechanisms of TR, the severity of TR, and a more detailed evaluation of the extent of right-heart remodeling.

Transthoracic echocardiography (TTE) is used for the initial evaluation of the tricuspid valve. With 2D transthoracic echocardiography, all three leaflets cannot be seen concurrently. For comprehensive tricuspid valve evaluation, multiple views acquisition is necessary. The anterior leaflet is visualized in the RV inflow view. The short-axis view of a posterior leaflet is most commonly seen next to the RV free wall. The septal leaflet is adjacent to the septum in the 4-chamber apical view.[12] Annular dimension should be evaluated in the 4-chamber view, in end-diastole. A significant annular dilation is defined as ≥ 4 cm according to ACC/AHA guidelines.[13] With 3D echocardiography, there is a distinctive opportunity to evaluate all leaflets simultaneously.

Transesophageal echocardiography has a less established role in evaluating the tricuspid valve. TEE provides superior resolution than TTE and can be applied in the case of suboptimal transthoracic images where leaflet morphology can be assessed with more detail. Also, similarly to 3D echo, all three leaflets can be seen concurrently in the TEE transgastric images. The application of color and spectral Doppler increases the sensitivity of the detection of tricuspid valve regurgitation. It helps to establish the mechanism of valve dysfunction and allows further quantification of the regurgitation. TEE also has a significant role in preprocedural planning and intraprocedural guidance during various interventional therapies for TR. Echocardiographic findings in severe TR are described in Table 1.

There is a limited role of cardiac MRI in evaluating the tricuspid valve morphology. Nevertheless, it can be advantageous in congenital disorders, e.g., Ebstein's anomaly or myxomatous valve degeneration.[14] Assessment of RV size and function constitutes an integral part of evaluating the patient with TR. RV dilation is expected in case of severe tricuspid valve regurgitation. Right ventricle dysfunction is a complication of chronic untreated severe TR. With 2D echocardiography, tricuspid annular plane systolic excursion (TAPSE) and systolic annular tissue Doppler velocity (S') can be used to help to assess the right ventricle function. With 3-D echocardiography, right ventricle size and function assessment are more accurate as they bypass the RV shape's geometric assumption. Current guidelines recommend 3D picture acquisition of the RV whenever feasible. Nevertheless, cardiac MRI is still a gold standard for right ventricular size and function quantification.[15]

PROPER TIMING AND PATIENT SELECTION

It identifies ideal candidates that could have prognostic and clinical benefits from transcatheter tricuspid valve treatment. Patient screening by a multidisciplinary heart team is paramount to optimize results. The appropriate timing to perform these procedures plays an important role, and more clinical data is needed for further clarification of this aspect.

Though echocardiogram is used to assess the morphology of TV and grading of TR, CT-angio is emerging for patient selection and procedural planning. Angio-CT helps to: (1) assess dimensions of the tricuspid annulus and anatomy; (2) measure the angle between inferior vena cava (IVC), superior vena cava (SVC), and TV plane; (3) measure SVC and IVC dimensions; and (4) assess the proximity of the RCA to the valve annulus and (5) identify target site geometry for annuloplasty devices.[11,16]

MANAGEMENT OF TRICUSPID REGURGITATION

While medical management with diuretics and aldosterone antagonists has a role in treating TR, surgical intervention remains the definitive treatment and the gold standard for those with severe disease.[17] This includes repair or replacement of the valve, which can be performed by minimally invasive procedures. Unfortunately, however, surgical interventions can have high mortality rates, leading to many patients not receiving effective therapy for tricuspid valve disease.[1] In deciding which treatment is best, it is essential to consider the etiology of the TR, as those with functional TR (i.e., leaflets appear macroscopically normal) secondary to right heart dysfunction or dilation, pulmonary hyperten-

Table 1 Echocardiographic findings in Severe TR.

Parameters	Findings in severe TR
Valve morphology	Severe lesions like Flail leaflet, severe retraction, large leaflet perforation, large vegetations, papillary muscle rupture
Interventricular septum	Paradoxical motion or volume overload pattern
Color flow TR jet	Holosystolic jet deep into the right atrium, or eccentric jet impinging the atrial wall
Flow convergence zone	Large and holosystolic
CW TR jet density/contour	Dense signal, early peaking signal with triangular shape
Inferior venacava	Usually dilated with reduced respirophasic variation
Right ventricle and right atrium	Usually dilated
Tricuspid annulus	> 40 mm^2/m^2 or 21 mm^2/m^2
Color flow jet area	> 10 cm^2
Vena contracta	≥ 0.7 cm
Proximal isovelocity surface area radius	> 0.9 cm
Hepatic vein flow	Systolic flow reversal
Tricuspid inflow	Dominant E-wave ≥ 1.0 m/s
Effective regurgitant orifice area	≥ 40 mm^2
Regurgitant volume	≥ 45 mL

CW: continuous wave; TR: tricuspid regurgitation.

sion, or left-sided heart dysfunction require special considerations. Specifically, severe right ventricular dysfunction, pulmonary hypertension, hepatic dysfunction, and previous left-sided valvular heart surgeries present significant challenges and may suffer greater morbidity and mortality related to surgical treatment.[18] For this reason, and to meet the unmet needs of those high-risk surgical patients needing treatment, percutaneous (or "transcatheter") interventions are a rapidly evolving alternative management option.

Both surgical and percutaneous strategies must consider the presence of other valvular diseases. Approximately 20%-30% of patients receiving surgical intervention for left-sided valvular heart disease present with concurrent severe TR. Current US guidelines state that it is best to treat both the left-sided valvular disease and the TR when operating on this cohort of patients.[8,13] Broadly, patients who require left-sided valvular heart surgery also have concurrent severe TR (primary or secondary cause), those with mild to moderate secondary regurgitation with annulus dilatation, or those with signs of right heart failure are candidates for right-sided valve surgical repair.[1,19] This approach will likely improve long-term right ventricular remodeling and reduce heart failure symptoms.

While these guidelines are important, the guidelines for the surgical management of those patients with isolated TR are less clear. In patients with no need for left-sided valvular heart surgery (i.e., no left-heart pathology to surgically repair), right-sided surgical repair may be appropriate in specific circumstances. Namely, surgery may be indicated if a patient with severe primary TR is symptomatic, if there is severe secondary TR in a symptomatic patient without severe right or left ventricular dysfunction and without pulmonary hypertension, or if the patient is asymptomatic with evidence of progressive right ventricular dysfunction or dilatation.[1,19] It is recognized that these patients with isolated TR have poor outcomes, with the scarce available data demonstrating average operative mortality of 8%-10%.[6] For these patients who are poor surgical candidates, novel therapies, such as percutaneous approaches, should be considered as a treatment possibility. Likewise, percutaneous intervention is an alternative for those who require repeated tricuspid valve surgery.

Classical surgical management of TR began with the Kay technique of suture annuloplasty.[20] In this approach, sutures are placed in the posterior commissure of the valve, which excludes the posterior leaflet to create a bicuspid valve effectively. Similarly, the DeVega approach places two parallel sutures in a counterclockwise fashion (posteroseptal

to anteroseptal) around the tricuspid annulus, reducing the valve's diameter. Other surgical techniques include deploying a rigid or semi-rigid ring to restore normal physiologic anatomy and function to the valve and the "Clover Technique," where the center of the leaflets are sutured together. This effectively creates smaller orifices for blood flow.

The percutaneous intervention treatment options are often variations of the classical surgical treatment approaches; however, unique methods have become available in recent years. These percutaneous treatment approaches can be divided into four broad categories: vena cava valves, annuloplasty valves, coaptation devices, and transcatheter tricuspid valve replacement/implantation (Figure 1).

VENA CAVA VALVE APPROACH

Edwards Sapien Valve

SVC and IVC valve systems are deployed to decrease blood regurgitation into said veins instead of repairing or replacing the tricuspid valve. The Edwards Sapien XT valve, a valve mainly used to treat aortic stenosis but has an off-label use for severe TR, is used in the IVC to reduce regurgitation. This device has been used in at least 10 cases, with 9 of those cases seeing improvements in the pre-procedure New York Heart Association (NYHA) class and right ventricular function, according to data presented in 2015.[4,21] One case series of six patients with severe TR showed improvement in the degree of regurgitation in four of six patients.[22] However, four of six patients needed rehospitalization within six months of device implantation, suggesting that this device may be better suited for short-term palliative therapy than long-term management. Dreger, *et al*.[23] conducted a study of 28 patients comparing optimal medical treatment and inferior vena cava implants. At three months follow-up, although there were differences in NYHA, dyspnea, and quality of life for those receiving the caval implant, there were no statistically significant differences between the two groups. More trials, such as the HOVER trial regarding caval implant devices, are required to evaluate their efficacy.[24]

TricValve

The TricValve device, another caval implant system, is designed as a bicaval implant with two self-expandable valves, one going to the SVC and one in

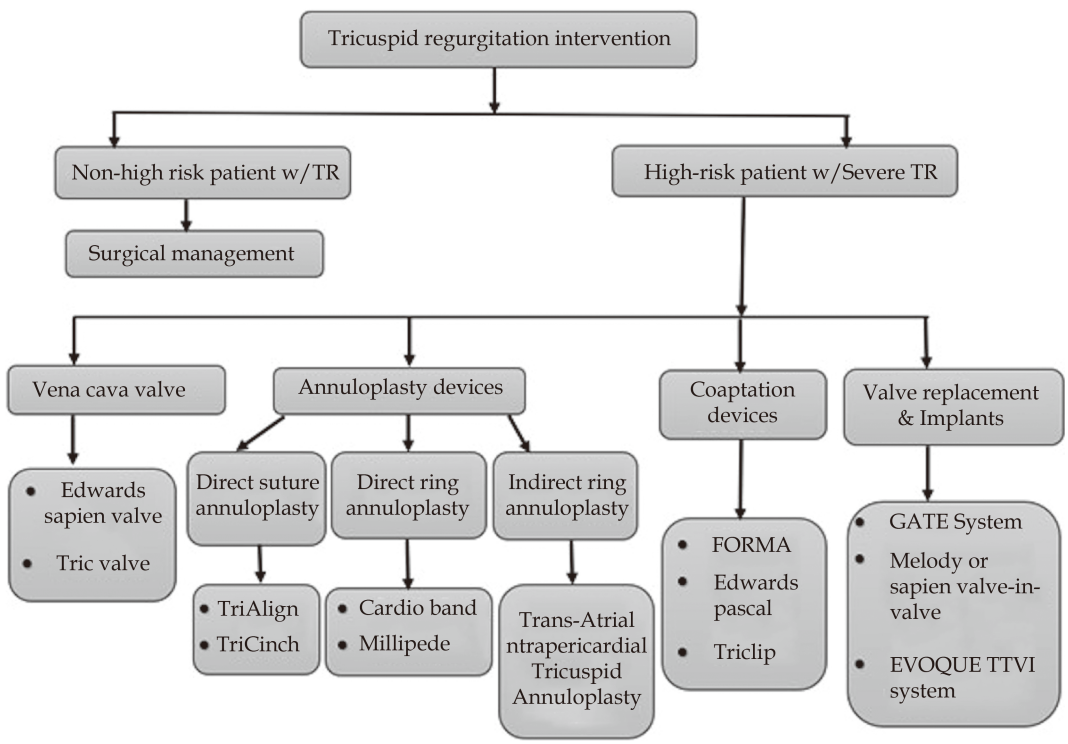

Figure 1 Classification of various available percutaneous interventions for tricuspid valve regurgitation. TR: tricuspid regurgitation.

the IVC. This device has been shown to provide significant hemodynamic improvement and relief of heart failure symptoms in a few patients.[4,5,21] Lauten, *et al*.[25] using both the TricValve and the Sapien XT device, showed improvement in TR-associated venous backflow and initial clinical disease. Both devices require more supporting data before making informed suggestions on their use in a clinical setting.

ANNULOPLASTY APPROACH

The current surgical therapy for functional TR is annuloplasty of the tricuspid valve, an intervention directed at correcting the annular dilation to restore normal annular anatomy and geometry. Annuloplasty can be approached via two techniques. The first, called suture annuloplasty, involves creating a functional bicuspid valve by suturing the posterior leaflet and commissures or suturing the endocardium at the posterior-septal anteroseptal commissures. The other technique, ring annuloplasty, involves the placement of a rigid or semi-rigid ring to control annulus dilation.[1]

Direct Suture Annuloplasty Devices

Suture annuloplasty devices have shown promising results. These include the TriAlign and TriCinch devices, minimally invasive annuloplasty, and pledget-assisted suture tricuspid annuloplasty.

TriAlign The TriAlign system is a percutaneous replication of the Kay surgical repair method, first implemented successfully in 2015.[26,27] An early feasibility study in the US, the SCOUT I study, has shown procedural success in 12 of 15 case patients using the TriAlign device at 30-day follow-up.[28] A significant reduction of the tricuspid annulus diameter, orifice area, and decreased right-sided heart failure symptoms were observed.[5]

TriCinch Another annuloplasty device, the TriCinch system, utilizes an implantable stainless-steel corkscrew fixated to the anteroposterior tricuspid valve annulus.[29] After implantation, the system is pulled toward the IVC via a Dacron band and anchored to the IVC, allowing the prolonged tension to remodel the anteroposterior annulus. The PREVENT study, an ongoing feasibility study of the TriCinch system, has shown improvements in TR when using the TriCinch device, specifical improvements in quality-of-life testing and functional status.[30] The procedural time to implant this device is relatively short, with a mean procedure time of 63 min. However, only eight patients have been enrolled, with 3 completing 6-month follow-ups; therefore, more data is necessary to evaluate the device's effectiveness.

Minimally invasive annuloplasty Minimally-invasive annuloplasty technology reduces the tricuspid valve annulus by utilizing a surgically-implanted, suture-less elastomer and anchors that apply self-tension to reduce the diameter. The Study of Transcatheter Tricuspid Annular Repair (STTAR) is enrolling patients to evaluate the efficacy of this device, with the minimally invasive arm of the study expected to be launched soon.[16]

Pledget-assisted suture annuloplasty The transcatheter pledget-assisted annuloplasty is a novel technology that reproduces the Hetzer suture technique in which two sutures and one pledget (a tiny bit of material) reduce the diameter of the annulus. Typically, the sutures are placed at the tricuspid annulus's mid anterior and posteroseptal aspects and are then tightened. Only one case of compassionate use has been reported.[4]

Direct Ring Annuloplasty Devices

Direct ring annuloplasty devices include the Cardioband and Millipede IRIS devices.

Cardioband Ring annuloplasty devices take a different approach. The Cardioband system, based on a method used to treat mitral regurgitation, is a transcatheter direct annuloplasty implant that is delivered transseptal to reduce the mitral annulus. It can be reversible and adaptable to the tricuspid annular geometry, allowing the ring's band to remain evenly distributed. Initial studies of this device in mitral regurgitation have proven it to be an effective device.[2] The TRI-REPAIR study, which uses the Cardioband system to address TR, showed a significant reduction in annulus diameter and TR regurgitation volume.[3] Of the 30 patients in the study, 28 were evaluated at 30-days and showed improvements in functional status with a reduction in NYHA class by at least one category; at 6-month follow-up, 15 of 25 showed improvement ($P < 0.001$). A stable reduction in annular dimensions was also seen in a statistically significant portion of these patients at 30-day, 6-month, and 2-year follow-ups.[6]

Millipede The Millipede device, a semirigid, complete adjustable ring, uses a design of 8 helical stainless-steel anchoring points for attachment to the tricuspid annulus.[11,31] This device is advantageous because of its ability to be repositioned and retrievable; however, the design of the anchors may increase the risk of complete atrioventricular node block. In a study of nine patients who received the device for mitral regurgitation, two of these patients also received the device implant for concurrent TR.[4,32,33] Both of those patients experienced a reduction of tricuspid annular diameter and TR grade (37% annular reduction with TR grade reduction from 4+ to 1+ in patient 1; 36% annular reduction with TR grade reduction from 3+ to 0 in patient 2).

Indirect Ring Annuloplasty Devices

Trans-atrial intrapericardial tricuspid annuloplasty The other annuloplasty approach, the trans-atrial intra-pericardial tricuspid annuloplasty (TRAIPTA), is a catheter-based repair system specifically designed to treat TR secondary to annular dilation. Utilizing X-ray fluoroscopy, a puncture in the right atrial appendage is made via a delivery device inserted in the atrioventricular groove. This allows the placement of a circumferential stitch that reduces tricuspid annular circumference and pathologic regurgitation after placement and correct application.[4] Rogers, *et al*.[34] demonstrated this device in a study of 16 Yorkshire swine. Of the 16 swine, 4 of which underwent processes to cause preprocedural functional TR, all had successful implantation of the device. The device showed a statistically significant decrease in the septal-lateral dimensions (49%, $P < 0.001$), the anteroposterior dimensions (59%, $P < 0.001$), annular area (59%, $P < 0.001$), and the annular perimeter (24%, $P < 0.001$). Important to note is that tricuspid leaflet coaptation length was also significantly increased (53%, $P < 0.001$). While this study is promising, other evidence of this technique is currently scarce.

COAPTATION APPROACH

The coaptation approach to the management of TR provides a platform for the native leaflets to close appropriately while occupying the regurgitant space.

FORMA

The FORMA system is a leading coaptation device, utilizing a passively expandable, foam-filled spacer anchored into the right ventricular myocardium, providing a surface for the valve leaflets to close the orifice.[30] This device has been successfully implanted in 16 of 18 possible patients through a compassionate use program.[16] Among 14 of the 16 patients who were followed up at 1-year, 86% improved NYHA functional class, quality of life measures, and 6-minute walk tests.[35,36] Likewise, a pretreatment classification of "severe TR" in 94% of patients was reduced to "moderate-to-severe or less" in 46% of the same population. Despite promising results, the US Early Feasibility Study suggests that more data is needed before this device becomes a mainstay of clinical treatment. The European Union and Canadian SPACER trials will hopefully provide such data and expand the current understanding of the FORMA device.[16]

TriClip

The TriClip device, based on the original MitraClip device, is another alternative coaptation technology that can treat TR. Designed to simulate an edge-to-edge Alfieri stitch technique, which involves a suture placed in the center of both mitral valve leaflets to create two mitral valve orifices, it has been proven effective for percutaneous treatment of mitral regurgitation. In 2016, the first known case of the MitraClip being used to treat TR was reported.[37,38] Early studies from Mehr, *et al*.[39] using a registry of 249 symptomatic TR patients (TriValve Registry) showed promise, with 72% of the patients in the study having an improvement in NHYA class by at least 1 grade. After using the device, this put most patients (69%) in the NYHA Class I + II categories, compared to 5% at baseline before device implementation. Since then, Nickenig, *et al*.[40] has reported the most extensive case series in the TRILUMINATE study, following 85 patients from 21 sites treated with the MitraClip. Of the patients evaluated for severity of TR at 30-days post-procedure (83 of 85), 86% had shown a reduction in TR by one grade or more.[36] Also, 30-day post-procedure assessments of NYHA class showed improvement. At baseline, 25% of the 83 patients were categorized as

NYHA class I or II, which increased to 80% at 30-day and 86% at 6-month follow-up.[40] At one-year follow-up, of the 62 evaluable patients, 87% showed a sustained reduction in TR by one or more grades, and 70% of the subjects were found to have moderate TR or less compared to 8% at baseline, 60% at 30 days. 83% of patients improved to NYHA class I or II (baseline 31%).[38,39] Among other notable outcomes in the 1-year follow-up of the TRILUMINATE study, the reduction in TR at 30-day follow-up was sustained at one year. When comparing the decrease in TR at 30-day and one-year follow-up, 35% of patients had a further reduction in TR grade, and 44% showed no change from their 30-day follow-up visit.[38] The study also showed that patients with severe TR at baseline were more likely to experience a reduction to moderate or less TR at 6-month and 1-year follow-up compared to those with "massive" or "torrential" TR, suggesting that treatment earlier in the disease may provide more benefit. Orban *et al*.[41] conducted a similar study of the MitraClip technology in 50 patients who presented with TR. Forty seven of 50 patients had successfully implanted the MitraClip device, with 46 of those having an immediate reduction in at least one TR grade. At 6-month follow-up, of the 39 patients with available echocardiography data, 35 showed a persistent decrease in their TR by at least one classification level. Likewise, 79% of all patients had improvement in at least one NYHA class compared to their baseline. Figure 2 shows an illustration of TEE-guided tri-clip implantation.

Edwards Pascal

The Edwards Pascal mitral valve repair system combines characteristics of both the MitraClip and FORMA systems, namely by using a 10-mm central spacer with two paddles and clasps. This design allows the single device to address the boundaries of the two devices when they are used separately.[16,42] In a multicenter compassionate use study, 23 patients were treated for moderate-to-severe or severe mitral regurgitation with promising results.[43] Following this study, first-in-man implantation of the device to address TR was completed. After implantation, the patient had clinical resolution of symptoms, improved quality of life score, and reduced regurgitation with reverse RV modeling, as evidenced by an echocardiogram.[44] In a non-randomized, compassionate use study by Fam *et al*.[42] of 28 patients undergoing treatment with the Pascal repair system, 26 were evaluated, and 23 of 26 had significant improvement in their NYHA class (2 died between the procedure and 30-day follow-up). Likewise, 6-min walk distances increased with the difference from pre-procedure walk distances being statistically significant ($P < 0.001$). The CLASP TR II Pivotal Trial, a randomized trial with patients either in a device arm or medical therapy arm, is currently underway and will provide more data on the role of the Pascal device and the edge-to-edge repair strategy.

TRANSCATHETER TRICUSPID VALVE REPLACEMENT AND IMPLANTATION

Transcatheter bioprosthetic tricuspid valve replacement is another theoretical approach to managing TR. However, this approach may prove problematic due to the IVC and the TC angle. For patients who may require repeat surgical procedures and those with degenerating bioprosthetic valves, transcatheter valve-in-valve methods may benefit. Available data suggest that these devices (either the Melody transcatheter pulmonary valve or the Sapien 3 transcatheter heart valve) are correlated with a significant improvement in functional status. However, no long-term outcome data is available.[11]

GATE System

Transcatheter tricuspid valve implantation (TTVI) using the GATE system is also being investigated. The GATE System utilizes a stent with right ventricular tines that grasp the tricuspid leaflets from the ventricular side of the valve in conjunction with atrial tines aligned perpendicular to the stent to provide a seal at the tricuspid annulus.[45] A compassionate use study of 30 patients from 10 institutions showed that of the 26 patients who underwent successful valve implantation. All of them had a reduction of TR by at least one grade (75% had a decrease by two or more grades). A significant 76% of the patients had mild or less TR on discharge.[46]

EVOQUE TTVI System

A similar approach using the EVOQUE TTVI sys-

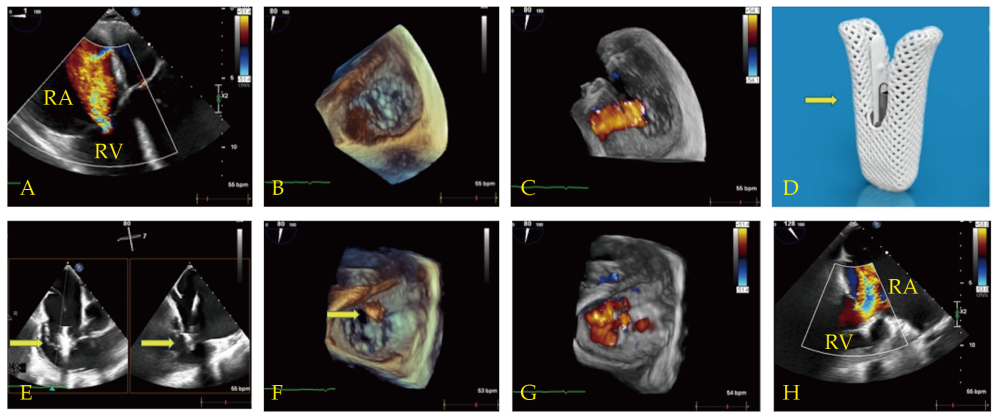

Figure 2 TEE guided tri-clip implantation. (A): 2DTEE demonstrating severe tricuspid regurgitation; (B): 3DTEE demonstrating tricuspid valve; (C): 3DTEE with color doppler imaging demonstrating severe tricuspid regurgitation; (D): Abbott TriClip; (E): 2DTEE with bi-plane mode demonstrating TriClip across the tricuspid valve; (F): 3DTEE demonstrating TriClip post-deployment; and (G): 3DTEE with color doppler imaging demonstrating improvement in tricuspid regurgitation post TriClip deployment; (H): 2DTEE improvement in tricuspid regurgitation post TriClip deployment. Arrow: TriClip; RA: right atrium; RV: right ventricle; 2DTEE: two-dimensional transesophageal echocardiogram.

tem has also been studied. The EVOQUE System uses a unique anchoring mechanism to stabilize the valve implant. The EVOQUE TTVI study showed promising results, with 23 of 25 study patients undergoing successful device implantation. TR was reduced to a grade of one or less in all 23 patients. At 30-day follow-up, 0 of 23 patients experienced death, stroke, myocardial infarction, valve reintervention, or heart failure hospitalization.[47] These short-term results are promising, and long-term, randomized clinical trials with larger sample sizes will aid in making this treatment more common in the future.

Other systems, such as the VDYNE valve, the LuX-Valve, and the Intrepid valves, are also innovative valve replacement devices, all currently being studied.[31] The VDYNE valve offers varying sizes to accommodate anatomic variety. The device, which is implanted through a novel side delivery system and a pop-off safety system in the event of afterload mismatch after implantation, will soon be undergoing first-in-human evaluation. The LuX-Valve, delivered via a right thoracotomy with a 32 French system, has shown a reduction to mild residual TR in 90.9% of successful implantation in initial first-in-human studies. It is also unique because it deploys two anterior leaflet clampers onto the native valve and one anchor on the interventricular septum, securing the valve without reliance on radial forces, as seen in other devices.[32,39,48] In a study of six patients with massive TR in whom the LuX-Valve was deployed, procedural success was 100% without mortality and complications during 30-day follow-up. The severity of TR improved significantly in all the patients. A 12-month follow-up showed a reduction in NYHA class and improvement of mean tricuspid valve transvalvular gradient in five patients. One patient with moderate paravalvular leakage died in postoperative three months due to non-improvement of the symptoms.[48] The Intrepid valve, initially developed for transcatheter mitral valve repair, has been adapted for TR and has received FDA breakthrough status (2020). Participants are being enrolled in trials for the device currently.[31]

VALVE-IN-VALVE AND VALVE-IN-RING IMPLANTS

Valve-in-valve devices allow an implanted system to be anchored onto a circumferential valvular ring, typically accomplished with either the Melody or Sapien valve devices. Transcatheter valve-in-valve implantation is an appealing approach in high-risk patients with bioprosthetic tricuspid valve failure needing redo surgery.[49,50] In a multicenter study of valve-in-valve implantation, 152 device implantations were attempted, with 150 successful. At follow-up, 76% of patients evaluated showed improvement in their NYHA classification by one category or more. At 30-day follow-up, 87% were either class I or II NYHA.[51] At 1-year follow-up, 17 patients had died, with one of those being related to the procedure.[4,51]

Valve-in-ring implantation has been reported as a

possible management approach; however, only four cases of such intervention have been reported, and there have been several challenges to this approach. Namely, the exact sizing of the prosthetic ring and the lack of native tricuspid annulus calcification, making it challenging to anchor an implant, are difficulties that must be addressed.[4] Figure 3 illustrates a TEE-guided tricuspid valve-in-valve implantation.

While more evidence is necessary to determine the long-term efficacy of transcatheter tricuspid valve replacement in TR, there is data to support that these transcatheter approaches improve functional status and reduce the severity of regurgitation. Likewise, comparing the surgical and transcatheter procedures to TR management would significantly affect the current guidelines.

CHALLENGES FOR TRANSCATHETER PLACEMENT OF THE TRICUSPID VALVE

Non-calcified TV apparatus needs larger valves for proper stabilization—angulation of the tricuspid valve with superior vena cava and inferior vena cava. Valve placement in the triangle of Koch increases the risk for complete AV blocks. The necessity for life-long anticoagulation is due to the low flow on the right side of the heart. One of the most important considerations and adverse effects in a transcatheter tricuspid valve replacement is the hemodynamic effect of a rather sudden repair of TR. Repair of the tricuspid valve could increase RV afterload due to the sudden increase in volume and pressure.[32] This could worsen right-sided heart failure and highlights the importance of proper patient selection for these procedures.

CONCLUSIONS

This review has delivered a broad overview of the literature on epidemiology and etiology of TR, anatomy of the tricuspid valve, pathophysiology, and diagnosis of TR. This paper summarizes various available percutaneous transcatheter interventions for TR. Isolated TV surgery remains infrequent due to high operative risk. Consequently, the prevalence of untreated TR patients increased significantly. Several less invasive transcatheter-based therapies have emerged as an alternative to surgery in high-risk patients in response to this unmet clinical need. These techniques have been rapidly evolving in the last few years. However, there is only preliminary data on TV valve percutaneous interventions. Randomized controlled trials with more significant numbers of patients and longer follow-ups are required to evaluate better the safety, efficacy, and superiority of these treatment options.

Overall, there is no well-established patient selection for tricuspid valve repair. The decision should not be made merely on the severity of the regurgitation. It should incorporate information about the etiology of the tricuspid valve dysfunction, signific-

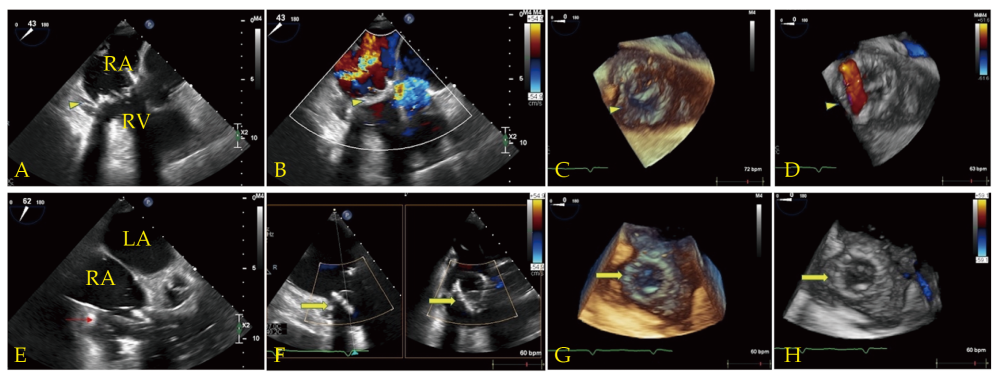

Figure 3 TEE-guided tricuspid valve-in-valve implantation. (A): 2DTEE demonstrating bioprosthetic valve in tricuspid position; (B): 2DTEE with color doppler imaging demonstrating severe tricuspid regurgitation; (C): 3DTEE demonstrating bioprosthetic valve in tricuspid position; (D): 3DTEE with color doppler imaging demonstrating severe tricuspid regurgitation; (E): 2DTEE demonstrating the deployment of the transcatheter bioprosthetic tricuspid valve-in-valve; (F): 2DTEE with bi-plane mode and color doppler imaging after valve deployment demonstrating a reduction in the tricuspid regurgitation; (G): 3DTEE demonstrating bioprosthetic valve in valve in tricuspid position; (H): 3D TEE with color doppler imaging demonstrating absence tricuspid regurgitation post valve in valve implantation. Arrow head: bioprosthetic valve in tricuspid position; red arrow: catheter across tricuspid valve; yellow arrow: bioprosthetic tricuspid valve in valve. LA: left atrium; RA: right atrium; RV: right ventricle.

ant pulmonary hypertension, and the surgical complexity of the repair.

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