Transcatheter Tricuspid Valve Intervention

A Review Article

by

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Transcatheter tricuspid valve intervention

I-Introduction

In the past two decades, the interest in tricuspid valve treatment has increased (Zack; et al., 2017), nevertheless only 5% of the population with severe tricuspid regurgitation receives a surgical treatment **(Stuge, et al., 2006)**. Patients with untreated TR have a poor prognosis **(Topilsky, et al., 2014),** and most of them receive lifetime medical therapy until intractable right heart failure and end-organ dysfunction appears. Regurgitation remains the principal pathology of the tricuspid valve and it is more often secondary rather than caused by a primary valve lesion (**Agarwal, et al., 2009).** Annular dilatation and increased tricuspid leaflet tethering in relation to right ventricular pressure and/or volume overload cause secondary TR. Left-sided heart disease, atrial fibrillation, or pulmonary hypertension are frequently involved in the pathogenesis of tricuspid regurgitation **(Asmarats, et al.,2018)**. All this evidence changed the management of tricuspid regurgitation to a more aggressive surgical approach, and the most recent guidelines recommend surgical repair of concomitant replacement during left valve surgery also in patients with tricuspid annular dilatation or recent signs of right heart failure with non-severe TR **(Baumgartner, et al., 2017)**. Despite the improvement in operative techniques, the in-hospital mortality in patients with combined surgery or isolated tricuspid regurgitation who underwent surgical replacement (12.6% respectively 7.1%) or repair (10.8% respectively 8.1%) is still high **(Alqahtani, et al., 2017)**. Moreover, previous tricuspid valve surgery recurrence of moderate or severe TR may be as high as 60% at 5 years (Kim, et al.,2013), and reoperation is necessary in approximately 20% of patients within 10 years after tricuspid valve surgery (Guenther, et al., 2008). While redo surgery is the treatment of choice for a degenerated bioprothesis or deterioration of a ring annuloplasty, it may be associated with a very high mortality

rate, reaching 35% at 30 days (**Bernal et al.,2005**) , particularly in patients with comorbidities.

Patients with tricuspid regurgitation, and high risk for surgery, were until recently predestined to conservative treatment. The promising results in aortic and mitral valve percutaneous interventions in high-risk patients have encouraged the development of percutaneous tricuspid interventions.

In the selection of patients with severe TR who may be candidates for transcatheter therapies, the following aspects need to be considered:

Anatomy of the TV and its relationships with surrounding structures (atrioventricular node, coronary sinus, right coronary artery [RCA]); Etiology of TR; Severity of TR; RV dimensions and function;

The specific anatomic and functional information of the TV, RV, and atrium, as well as venous access needed for each TV repair device.

Tricuspid Valve Anatomy

The TV is nearly vertical and oriented at approximately 45° to the sagittal plane, so that the margins of the valve are antero-superior, inferior and septal. Classically, three leaflets were described. However, the advancement in the field of percutaneous tricuspid procedures have generated renewed interest in the anatomy of the tricuspid valve complex. Several studies showed an important variability of the tricuspid leaflets number . (**Kawada, et al., 2018**).

the anterior leaflet is the largest, with a semi-circular shape and is almost always anchored to a single papillary muscle, which is attached to the free wall or the anterior wall of the right ventricle (RV). In functional tricuspid regurgitation, this zone is more prone to annular dilatation. The commissure between the septal and the anterior leaflets sometimes may have tendineous chords that attach to small papillary muscle (medial) arising from the interventricular septum (**Ho, et al.,2006**)

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The tricuspid annulus (TA) is a dynamic structure, which changes its shape and size during the cardiac cycle (approximately 20% reduction in annular circumference with atrial systole) (**Huttin, et al.,2016**)

. The tricuspid annulus approximates a number of important structures. The posteroseptal portion is limited posteriorly by the ostium of the coronary sinus and the inferior cavoatrial junction, which is separated by the ligament of Todaro and anteriorly by the atrioventricular node. The tricuspid annulus, ostium of the coronary sinus, and the atrioventricular node demarcate the triangle of Koch. The anteroseptal portion of the tricuspid annulus is in a close spatial relationship with the RV outflow tract and the noncoronary and right coronary sinuses. Finally, the segments of the tricuspid annulus covering the insertion of the anterior and posterior leaflets confirm the atrioventricular groove where the RCA courses. It has recently been shown that the anterior aspect of the tricuspid annulus can be very close to the RCA. In 7.5% of subjects, the RCA was within 2 mm of the anterior tricuspid annulus, which leaves at risk of compression during a surgical or percutaneous annuloplasty procedure (**Diez-Villanueva, et al., 2014**). The right atrial caval tricuspid isthmus is the area between the inferior vena cava and the TV, and at times, it is highly variable anatomically, with a large Eustachian ridge, concave deformities, and aneurysmal pouches (**Saremi, et al.,2008**).

Four chief anatomic structures surround the TV and are therefore at risk for impingement during transcatheter tricuspid interventions: the conduction system (atrioventricular node and right bundle of His coursing the membranous septum at 3 to 5 mm from the anteroseptal commissure, the right coronary artery (encircling the right atrioventricular groove ~5.5 mm from the septal and posterior portions,
7 mm from the anterior portion), the noncoronary sinus of Valsalva, and the coronary sinus ostium being an important landmark of the posteroseptal commissure. The TV

apparatus poses additional challenging issues to overcome: lack of calcium, angulation in relation to the superior vena cava (SVC and inferior vena cava (IVC), a trabeculated and thin right ventricle hindering a transapical approach, other presence of pre-existing cardiac implantable electronic devices (**Rodes-Cabau, et al., 2016**).

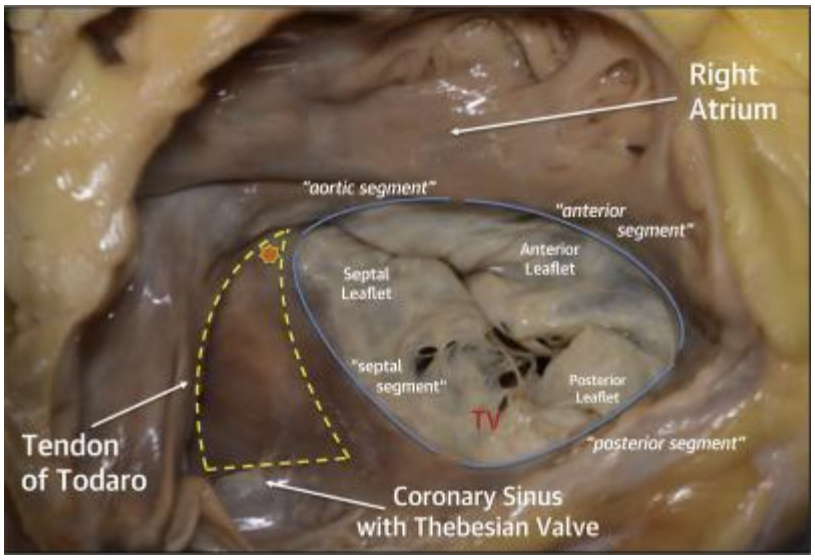

Figure 1 Tricuspid Valve and Surrounding Structures (**quoted from Asmarats , et al., 2018)**

Mechanism of Tricuspid Regurgitation

The pathophysiology of secondary or functional TR can be divided into three phases. In the first phase, left-side heart disease, pulmonary hypertension and atrial fibrillation may determine impairment of RV, with progressive dilatation, which can lead to dilatation of the tricuspid annulus. The coaptation is not affected ("body-to-body") and the TR is not significant. In the second phase, the progressive dilation of the RV and TA can result in a poor leaflet coaptation ("edge to-edge"), leading to progressive, significant TR. Finally, in the third phase, continuous distortion of RV geometry, especially on the anterior wall associated with tethering of the leaflets, will get worse with the degree of TR. The anterior and posterior leaflets, will lose

contact (“non coaptation”), determining dilation of the TA along its antero-posterior plane. The septal leaflet, anchored to the fibrous skeleton, is only partially involved in the dilation of the TA (**Dreyfus, et al.,2015**).

Imaging Evaluation

Echocardiographic screening

Comprehensive transthoracic (TTE) and transesophageal (TEE) echocardiography evaluation of the tricuspid valve is essential in diagnosing tricuspid regurgitation cause as well as for planning potential transcatheter tricuspid valve intervention (**Hahn RT,2016**).

On TTE, tricuspid valve morphology, leaflet tenting height, tricuspid regurgitation severity, right ventricular geometry and systolic function should be assessed based on the guideline recommended imaging windows and parameters (**Rudski, et al., 2010**). A more detailed evaluation of the tricuspid valve is also possible with the addition of modified dedicated valve views (**Addetia, et al., 2016**). Specifically, the anterior and septal leaflets are best visualized when the right ventricular inflow view includes the interventricular septum and in an anteriorly directed apical four chamber view (toward a five-chamber view). The posterior and septal leaflets are visualized on a posteriorly directed apical four chamber view (with the coronary sinus in view). The parasternal short axis view is more variable, but three-dimensional biplane imaging from this view can be used to localize specific leaflet pairs. An en-face

view of the tricuspid valve is possible as well, either from a three-dimensional volume or with two-dimensional imaging from a subcostal imaging window.

TEE is the mainstay for tricuspid valve intervention screening because of its key role in intraprocedural guidance (Fig. 2). Each transcatheter tricuspid valve repair solution has unique imaging needs, but also shares basic principles. The anteroseptal and posteroseptal commissures are generally best imaged from the mid or lower esophageal windows between 0–308 and 150–1808 (Fig. 2a–b). A two-dimensional en-face view of the leaflets can be obtained from a shallow transgastric position between 0 and 30º (Fig. 2c). Three-dimensional volumes can be reconstructed using multiplane reconstruction for specific imaging planes Fig. 2d).If adequate TEE imaging is not optimal, TTE or intracardiac echocardiography (ICE) can also be used for visualization of the leaflets relative to the device during a procedure (**Fam, et al.,2018**). However, current technology limits the ability for complete guidance and device orientation using these methods alone.

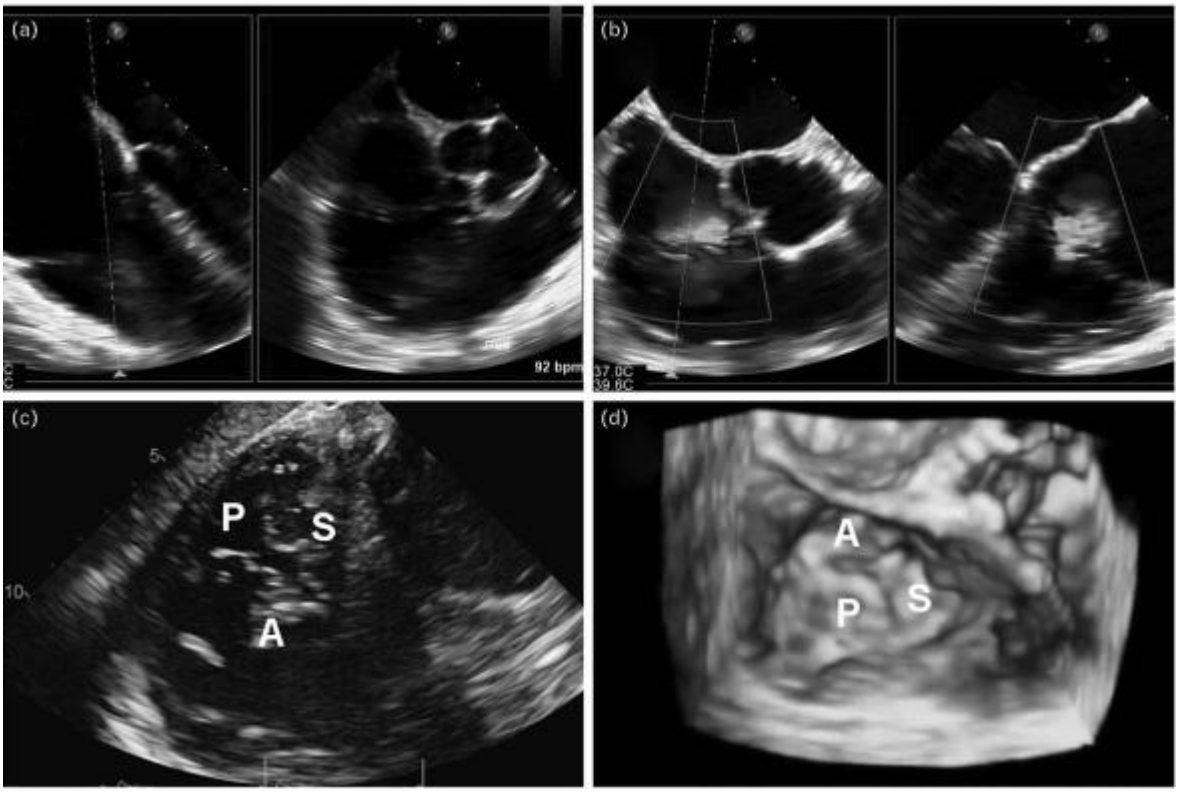

FIGURE 2. Echocardiographic views of the tricuspid valve for transcatheter tricuspid valve intervention screening. (a) Midesophageal biplane views (left panel: 08 view, right panel: 608 view) of the tricuspid leaflets and annular dimensions. (b) Color Doppler imaging using biplane imaging of the tricuspid valve. Leaflet pairs can be more accurately imaged and assessed using three-dimensional biplane imaging based off of a 60–90° imaging plane of the tricuspid valve. (c) Deep transgastric view of the tricuspid valve (left panel: 1008 right ventricular long axis view, right panel: 108 en-face tricuspidvalve view). (d) Three-dimensional volumes are often clearest from the lower esophageal window and can be manipulated to display an en-face surgical view, or reconstructed using multiplane reconstruction for specific imaging planes. **(quoted from Ho, et al., 2019)**

Multidetector computed tomography

Multidetector computed tomography can provide important insights into valve structure in patients with functional tricuspid regurgitation and is complementary to echocardiography in terms of planning for transcatheter tricuspid valve procedures. Specifically, this modality can provide additional anatomic details of the tricuspid valve annulus (geometry and dimensions), adjacent cardiac structures (such as

proximity of the right coronary artery) and caval veins. It can also help define intraprocedural fluoroscopic angles of coplanarity to the tricuspid valve annulus (**Naoum, et al.,2017**).

Computed tomographic (CT) imaging has become one of the most important imaging modalities during pre-procedural planning for TTVI, because it provides valuable anatomic information of the TV apparatus, which often is difficult to assess by echocardiography owing to its complex geometry and anterior position in the chest. The CT gives information regarding tricuspid apparatus morphology, landing zone geometry, annular dimension, presence of calcification, anatomic relationships with the surrounding structures, evaluation of the risk of right ventricular outflow tract obstruction, and it can also predict the best fluoroscopic projection (Pighi, et al., 2018).

The evaluation of RV function using cardiac magnetic resonance (CMR) is very important in the decision-making process. CMR imaging represents the gold standard for quantifying right ventricular volumes and function (Saremi, et al., 2015).

Right heart catheterization should be performed when needed to evaluate the pulmonary vascular pressures/ resistances.

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TABLE 2 Transcatheter Tricuspid Valve Interventions and Imaging Needs

Transcatheter Tricuspid Valve Intervention System	Clinical Data	Patient Selection: Imaging Questions	Imaging Technique
Heterotopic transcatheter valve implantation	HOVER trial TRICAVAL trial	Confirmation of severe tricuspid regurgitation Assessment of right ventricular systolic function Dimensions of caval vein* Distance from the inferior cavoatrial junction to the first hepatic vein†	Echo, CMR Echo, CMR MDCT MDCT
Direct tricuspid annuloplasty Trialign Tricinch Cardioband	PTVAS SCOUT and SCOUT II PREVENT TRI-REPAIR	Confirmation of functional severe tricuspid regurgitation Course of the right coronary artery along the atrioventricular groove Distance between the right coronary artery and the tricuspid valve annulus‡ Lobe of the right atrial appendage oriented anteriorly Demarcated atrioventricular groove	Echo, CMR MDCT MDCT MDCT MDCT
Indirect tricuspid annuloplasty TRAIPTA	Experimental	Location of the epicardial coronary arteries in relation to the atrioventricular groove	MDCT
MitraClip	European registry	Confirmation of severe tricuspid regurgitation Anatomy of the tricuspid valve with the largest effective orifice regurgitant area Coaptation, length, and tethering of the tricuspid leaflets§	Echo, CMR Echo Echo
FORMA Spacer	Feasibility study (NCT02471807) SPACER (NCT02787408)	Confirmation of severe tricuspid regurgitation Anatomy of the tricuspid valve with the largest effective regurgitant orifice area‖ Tricuspid annulus dimensions Right ventricular dimensions Distance of the tricuspid valve annulus plane to the right ventricular septal free wall groove Dimensions of the left subclavian and axillary veins#	Echo, CMR Echo Echo, MDCT Echo, CMR, MDCT Echo, CMR, MDCT MDCT
Transcatheter valve-in-valve or valve-in-ring	Ongoing registry	Confirmation of severe dysfunction of bioprosthesis or failing tricuspid annuloplasty Mechanism of failure Size of the sewing ring	Echo Echo Echo, MDCT

*Diameters of the inferior and superior vena cava may reach 35 and 40 mm, respectively (49,50). †In severe TR, mean distance between the inferior cavoatrial junction and the most superior hepatic vein is 14.1 ± 5.4 mm (18). ‡A distance between the right coronary artery and the tricuspid valve annulus of ≤2.0 mm is considered less favorable (18). §A severe coaptation defect (>20 mm) is considered an exclusion criterion for Mitraclip (51). ‖Forma spacers are available in 12- and 15-mm diameters (52,53). #Vascular access is achieved through a 24-F vascular sheath (52,53).

CMR = cardiac magnetic resonance; Echo = echocardiography; HOVER = Heterotopic Implantation of the Edwards-Sapien XT Transcatheter Valve in the Inferior Vena Cava; MDCT = multidetector row computed tomography; PREVENT = Percutaneous Treatment of Tricuspid Valve Regurgitation With the TriCinch System; PTVAS SCOUT = The Early Feasibility of the Mitralign Percutaneous TV Annuloplasty System; TRAIPTA = transatrial intrapericardial tricuspid annuloplasty; TRICAVAL = Treatment of Severe Secondary Tricuspid Regurgitation in Patients With Advanced Heart Failure With Caval Vein Implantation of the Edwards Sapien XT Valve.

A PRACTICAL PATIENT SELECTION ALGORITHM

On the basis of devices available and research to date, we propose the following patient selection algorithm (Fig. 4) when considering transcatheter tricuspid intervention. It incorporates important clinical First, patients should undergo review by a multidisciplinary heart valve team. This should include optimization with evidence-based medical and device therapy for left-sided myocardial or valve disease in the setting of functional tricuspid regurgitation.

Titration of diuretics as tolerated to relieve congestive symptoms should be attempted, even though the literature suggests that tricuspid regurgitation severity does not often decrease with diuretics (23% of patients) and clinical outcomes remain unchanged (**Konstam, et al., 2018**)

. Next, significant competing comorbidities should be assessed, especially those that make clinical benefit unlikely. If the life expectancy of an individual is less than 1 year and the underlying cause cannot be treated, the risk to benefit comparison may favor conservative management over an invasive procedure when considering the overall impact to the patient. This evaluation should include the likelihood of procedural success based on anatomic factors, the expected symptom benefit with an improvement in tricuspid regurgitation severity and frailty assessment. Some clinical comorbidities that may limit the benefit of a transcatheter repair include diagnoses such as decompensated end stage liver disease (Child–Pugh B and C), dialysis-dependent end-stage renal disease, severe lung disease, fixed severe pulmonary hypertension, significant neurologic dysfunction, active malignancy with poor prognosis and progressive cardiac amyloidosis. The heart valve team should then have a comprehensive understanding of the cause of severe tricuspid regurgitation, including a detailed anatomic assessment of the valve, annulus, subvalvular apparatus, pulmonary pressures and right ventricle. This is generally best assessed with TTE and TEE using protocols that include focused views of the valve in its entirety (**Hahn, 2016**). All current repair procedures rely heavily on TEE image guidance. Therefore, the ability to obtain good quality imaging is important to note. If image quality on TTE or TEE is inadequate, ICE can be considered for intra- procedural guidance. However, current technical limitations in sector width and three-dimensional imaging capabilities mean that this option generally requires specific expertise and may still need to be combined with TTE or TEE. Additional information from MDCT or cardiac magnetic resonance imaging may contribute to the understanding of certain anatomic details and accurate assessment of right ventricular systolic function (**Naoum, et al., 2017**)

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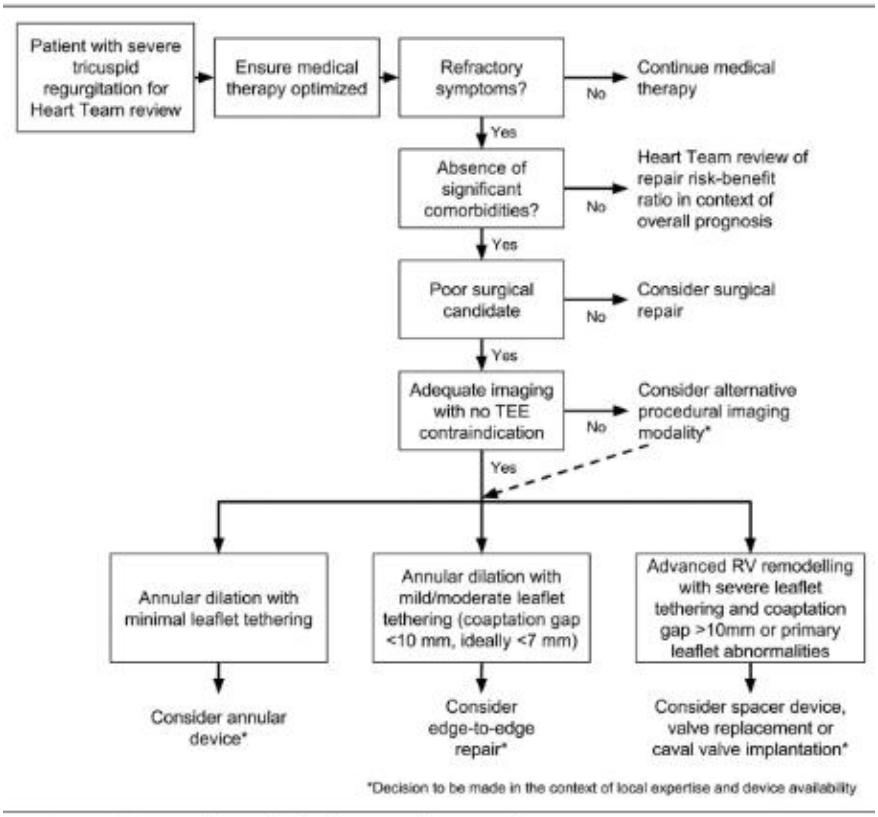

IRE 3. Proposed patient selection algorithm for transcatheter tricuspid intervention.

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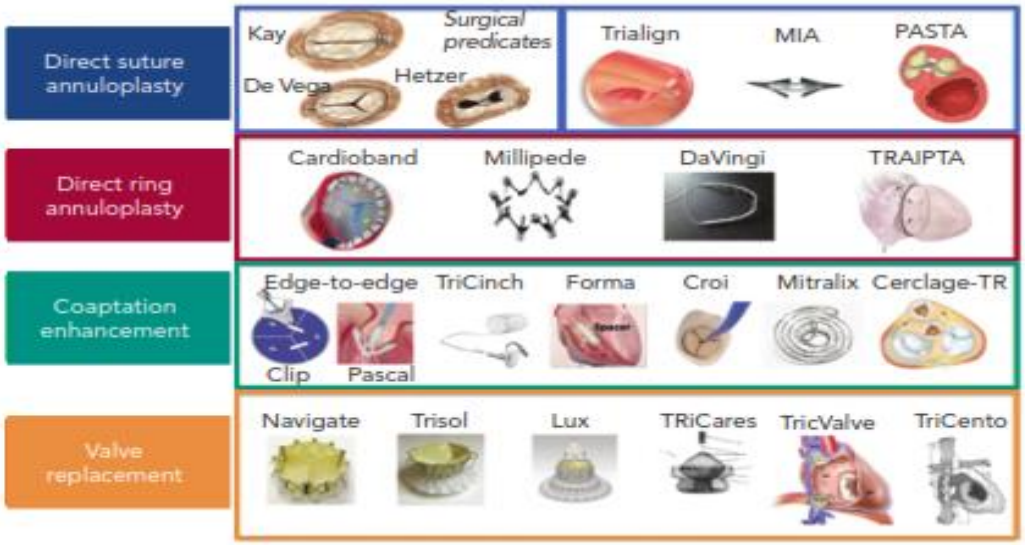
Evolving Transcatheter Options for Tricuspid Regurgitation Treatment

There are two main approaches with different subgroups that exist for percutaneous TR treatment – repair (i.e. leaflet approximation or annuloplasty) and replacement (in the orthotopic or heterotopic position; Figure 4).

Transcatheter tricuspid valve intervention



MIA = minimally invasive annuloplasty; PASTA = pledget-assisted suture tricuspid annuloplasty; TRAIPTA = transatrial intrapericardial tricuspid annuloplasty.

Repair

Leaflet Approximation/Coaptation Devices

MitraClip in the Tricuspid Position

The MitraClip system (Abbott Vascular, Santa Clara, CA), is originally known for the treatment of mitral regurgitation, but his off-label use for the treatment of TR has increased in the last years and is nowadays the most used transcatheter therapy for the treatment of isolated severe TR or combined severe TR and severe mitral regurgitation (MR) (**Taramasso, et al., 2019**).

It is formed by a clip delivery system (CDS) and a steerable guide catheter. The CDS includes the detachable clip, a cobalt-chromium polyester-covered implant with 2 arms that can be opened and closed by control mechanisms on the CDS, and on the inner part of the clip there are 2 grippers. Each gripper matches up to each arm, and their combination helps to stabilize the leaflets.

Despite the considerable and satisfactory results at mid-term follow-up, the MitraClip therapy has not been fully accepted for tricuspid therapy, because of some remaining criticalities, such as the insertion of a long device through trans-jugular

vein, furthermore the anatomy of the TV (three-leaflets and their different tissues properties) and the presence of big annular dilatation. Two types of techniques have been described for the treatment of severe TR, and they have comparable results.

• TOT technique, a triple-orifice technique: clips are placed between the septal and anterior tricuspid leaflet or between the septal and posterior tricuspid leaflet,

• BT technique, a bicuspidization technique: clips are placed between the septal and anterior tricuspid leaflet

The BT technique for the treatment of severe TR is used more than the TOT technique and the reason behind it, is that the BT technique seems to be more technically feasible (**Braun D, et al., 2018**).

Many studies have shown a significant improvement of the quality-of-life measurements after the implant of the clip, such as NYHA functional class and six minutes walking distance. Also, after the device implantation in patients with severe TR, an improvement of at least 1-grade of the severity of TR has been seen in >90% of the treated patients. Many studies also calculated the death rate at 12 months, 6 months and 30 day, and they were respectively 37.5%, 16% and 2.8% (**Orban, et al., 2018**).

Actually, the TRILUMINATE trial, is an ongoing prospective, single-arm multicenter study, that wants to evaluate the effectiveness and the safety of this device for the treatment of TR in a specific group of patients, namely those who have a >2+ symptomatic TR, under medical therapy and that are suitable for a transcatheter intervention [**NCT03227757, 2018**).

PASCAL

The PASCAL device was developed in order to treat mitral regurgitation. It has a 10mm central spacer, that fills the regurgitant orifice area of the valve and it attaches to the valve leaflets by two paddles, designed to maximize leaflet coaptation, and

clasps. The combination of spring-loaded paddles and clasps allow a uniform distribution of load over the entire surface of the inserted leaflets. Furthermore, the tip of the paddle has a convex curvature in order to reduce tension on the valve leaflets. The device is repositionable and recapturable.

Results of the first-in-human study show that the PASCAL system has a high rate of technical success in 23 patients with moderate-severe mitral regurgitation with a significant reduction of mitral regurgitation severity.

Recently, it has been published the results of 12 patients treated for their TR with the PASCAL device: 92% of the patients had a significant reduction of TR. An improvement of the NYHA functional class was also seen. Moreover, it has been recently reported a case of an 82-year-old woman with torrential TR and NYHA IV functional class with severe dyspnea, fatigue, ascites and peripheral edema, who was treated successfully using PASCAL device. Results at 1 month showed a significant reduction of TR to mild and an increase in quality-of-life measurements, with an improvement in NYHA functional class to II, improvement of the six minutes walking test, as well as an improvement of the general clinical situation, with the resolution of ascites (**Fam, et al., 2018**).

FORMA

The FORMA Repair System (Edwards Lifescience, Irvine, USA) is a device which is composed by two main components: a spacer unit and a rail. The spacer unit is a round and shaped balloon, 42 mm long and the suitable diameters are 12mm, 15 mm or 18mm. It can be inserted in two different ways: via the subclavian or the axillary vein. The spacer is inserted across the valve, by the use of a rail, and once it is in place, the leaflets of the native valve have a new surface for coaptation and therefore reducing the tricuspid regurgitation.

The whole system is then anchored to the endocardium of the left ventricle with a 6 curved prongs nitinol anchor, specially designed for not exiting into the pericardial space. The result is a reduction in the effective regurgitant orifice area (EROA).This system is implanted under general anesthesia with the transesophageal echocardiographic monitoring.

The implant procedure can be divided into 4 steps (**Perlman and Dvir. 2018**):

1. Venous access: most commonly through the left subclavian vein
2. Anchoring: the aim is to anchor the rail to the lateral wall of the RV close to the interventricular septum.
3. Spacer positioning: after the anchoring the spacer slides down into the TV orifice, until the monitoring confirms the regurgitation reduction
4. Rail fixation and access closure

Recently, the echocardiographic and clinical results of the first in-human, multicenter study have been published. At 1 year, apart from 1 device thrombosis out of 15 patients (7%), there were no significant complications in the study population, such as infections, arrhythmias, device dislocation or death [31-33].

This study also showed significant improvement in the echocardiographic imaging and in the quality-of-life measurements in the 14 patients with successfully implanted device. Of these 14 patients, an improvement of 18 points of the Kansas City Cardiomyopathy Questionnaire (KCCQ) has been reported (p=0.02), as well as an improvement in the average six minutes walking distance, 84m more compared with the preoperative phase (p = 0.03). Furthermore, 79% of the 14 successfully implanted patients were in NYHA functional class I/II after the device implantation. In echocardiography imaging, in 69% of patients at 30 days (p=0.001) and in 46% of patients at 1 year (p=0.01), a significant reduction to moderate-severe or less of tricuspid regurgitation has been seen. Some criticalities have been described for this

device. The main critical point is that often the regurgitant orifice area is huge in patients with severe FTR and therefore, very large device would be required in order to fill such a large gap. Additional studies are required in order

to better understand the efficacy and the safety of this device. In this regard there are two ongoing studies: the early Feasibility Edwards Study and the Repair of Tricuspid Valve Re- gurgitation Using the Edwards TricuSPid TrAnsCatheter REpaiR System (SPACER) trial (**NCT02471807, 2018 and NCT02787408, 2017**)

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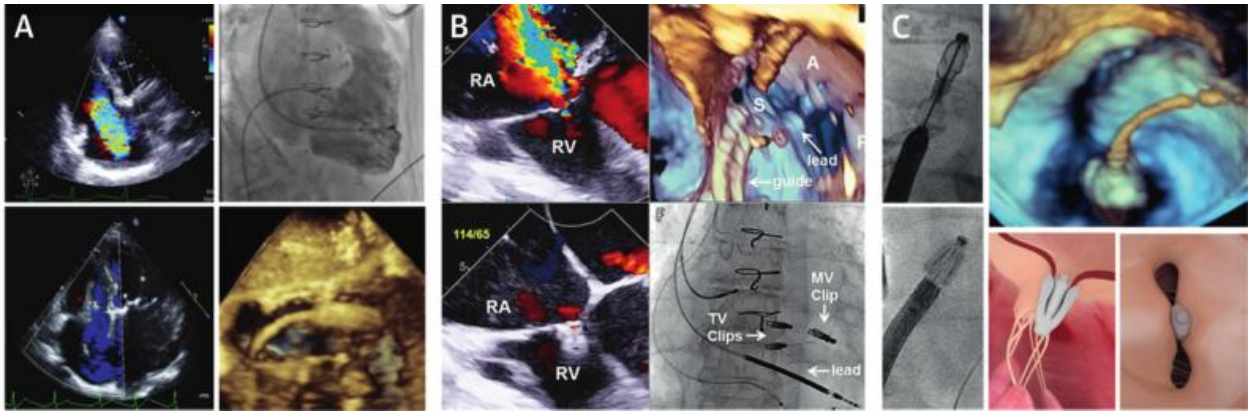


Figure 5 Figure Coaptation Devices

(A) Forma Repair System. Two-dimensional transthoracic echocardiography before and after device implantation, fluoroscopy, and 3-dimensional transthoracic echocardiography. (B) Interventional edge-to-edge repair with the MitraClip system in a patient with a pacemaker lead. Intraprocedural 2-dimensional and 3-dimensional transesophageal echocardiographic and fluoroscopic views. Reprinted with permission from **Fam et al. 2017**. (C) Pascal repair system. Fluoroscopy showing the unfolded and folded Pascal device sequentially; 3-dimensional transesophageal echocardiography and illustration showing double-orifice valve after deployment. Reprinted with permission from **Praz et al. 2017**

Annuloplasty devices

Cardioband TV reconstruction system

The Cardioband (Edwards Lifesciences, Irvine, CA, USA) is a polyester sleeve with radiopaque markers spaced 8 mm apart. The sleeve contains a pre-mounted contraction wire connected to an adjusting spool **(Messika-Zeitoun , et al.,2019**

). Twelve to seventeen anchors are implanted through the sleeve. Once the last anchor is delivered, the implant is then contracted using a size adjustment tool. The Cardioband has been implanted under compassionate use in 5 patients with functional TR with satisfactory results—23% to 45% reduction of the TA diameter and 50% to 70% reduction of the EROA without any procedure-related serious adverse events (**Mangieri , et al.,2018**).

The Cardioband system received Conformité Européene (CE) mark approval in April 2018 based on results of the TrIcuspid Regurgitation RePAIr With CaRdioband Transcatheter System (TRI-REPAIR) study, which enrolled 30 patients with NYHA functional class = II and moderate or greater functional TR (Nickenig, et al.,2019). Technical success was 100%. At 6 months, the Cardioband system resulted in average reductions of annual septolateral diameter of 9% ($P<0.01$), proximal isovelocity surface area EROA of 50% ($P<0.001$), and mean vena contracta width of 28% ($P<0.001$) compared with baseline (**Nickenig, et al.,2019**). LVSV increased from 59.2±19.7 to 64.5±12.1 mL ($P=0.07$) and 61.1±17.7 to 64.6±11.7 mL ($P=0.26$) after 30 days and 6 months, respectively (Nickenig, et al.,2019). The mean 6MWD increased by 60 m ($P=0.004$), KCCQ score improved by 24 points ($P<0.001$), and 76% of patients improved by at least 1 NYHA functional class with 88% in NYHA functional class I or II at 6 months.

The echocardiographic and improvements were sustained at 1 year follow-up (**Kreidel, 2019**).

The primary safety endpoint of major serious adverse events (a composite of death, myocardial infarction, cardiac tamponade, device-related cardiac surgery, and stroke) occurred in 13.3% of patients at 30 days (Nickenig, et al.,2019). All-cause mortality rate was 10%±5% at 6 months and 17%±3% at 1 year (**Nickenig, et al.,2019 and Kreidel, 2019**).

The Transcatheter Repair of Tricuspid Regurgitation with Cardioband TR System Post Market Study (TriBAND) is a European, prospective, single-arm, multicenter post-market follow-up study to assess the safety and efficacy of the Edwards Cardioband TR system in patients with symptomatic, chronic moderate to severe (=2+) functional TR (NCT03779490, 2019). The study is expected to enroll 150 patients who will be followed up at 30 days, 6 months, and annually up to 5 years. Thirty-day results of the US Edwards Cardioband Tricuspid Valve Reconstruction System Early Feasibility Study, which enrolled 15 patients with symptomatic chronic functional TR of moderate or greater severity, were recently presented (26). The mean age of patients was 80±8 years, 73% were women, and 73% were in NYHA functional class III or IV at baseline (**Lim, 2019**). Technical success was 93.3%. At 30 days, the Cardioband system resulted in average reductions of annual septolateral diameter of 14% ($P<0.001$), proximal isovelocity surface area EROA of 40% ($P<0.018$), and mean vena contracta width of 28% ($P<0.001$) compared with baseline. The mean 6MWD increased by 7 m (P=NS), KCCQ score improved by 13 points ($P=0.015$), and 64% of patients were in NYHA functional class I or II at 30 days ($P=0.047$) (26). Thirty-day mortality was 0%. Serious adverse events included RCA constriction in 1 (6.7%) patient and severe bleeding in 5 (33.3%)

patients (**Lim, 2019**). The ACTIVE TR US Pivotal Trial is expected to begin in late 2019.

TriAlign

The TriAlign device (Mitralign Inc., Tewksbury, MA, USA) is a transcatheter suture-based tricuspid annuloplasty system that attempts to replicate the results of the current modified Kay procedure, which has shown long-term efficacy similar to those of other surgical TV repair methods (**Schofer, et al.,2015**).

The posterior leaflet is plicated using 2 pledgets that are positioned at the anteroposterior and septal posterior commissure and then sutured together using the dedicated plication lock device. A distance of 25–28 mm between the 2 pledgets is recommended (**Besler, et al.,2018**). In case of suboptimal results, a second pair of pledgets can be implanted to obtain a consistent reduction in annular dimensions. The feasibility and safety of the TriAlign system was evaluated in 15 patients with NYHA functional class = II and moderate or greater functional TR enrolled in the Transcatheter Tricuspid Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation (SCOUT) trial (29). Technical success rate at 30 days was 80%. Three patients had single-pledget annular detachments that did not necessitate reintervention. In the remaining 12 patients, the TriAlign system significantly reduced TA diameter and EROA, with significant increase in LVSV. In the intention-to-treat cohort, there were significant improvements in NYHA functional class (=1 class, P=0.001), Minnesota Living with Heart Failure Questionnaire (MLHFQ) (47.4±17.6 to 20.9±14.8; P<0.001), and 6MWD (245.2±110.1 to 298.0±107.6 m; P=0.008). Data from the TriValve Registry on 18 patients who underwent TV repair with the TriAlign system demonstrated procedural success rate of 69.2% and zero deaths at 30 days. The Safety and Performance of the TriAlign Transcatheter Tricuspid

Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation (SCOUT-II) is an ongoing prospective, single-arm, multicenter, open-label study that will enroll up to 60 patients from up to 15 sites in Europe and US (**NCT03225612, 2018**). The primary endpoint is 30-day all-cause mortality.

TriCinch

The TriCinch system (4Tech Cardio Ltd, Galway, Ireland) reproduces the Kay procedure by cinching at the anteroposterior commissure, thus reducing septolateral dimensions. The TriCinch system consists of two components: (I) a stainless-steel corkscrew implant, to be placed in the anterior TA, in proximity to the anteroposterior commissure, and (II) a self-expanding nitinol stent that is deployed below the hepatic region of the inferior vena cava (**Rosser, et al.,2016**). The safety and efficacy of this device was investigated in the Transcatheter Treatment of Tricuspid Valve Regurgitation with the TriCinch System™ (PREVENT) first-in-man feasibility study (NCT02098200 ,2019). Among the 24 patients treated, procedural success rate was 85%. Reasons for unsuccessful procedure included hemopericardium requiring interruption of the procedure (n=2) and late detachment of the anchor (n=4) (Giannini and Colombo, 2019). Among the 14 patients who underwent TV repair with the TriCinch system in the TriValve Registry, procedural success rate was 62.5% with zero deaths at 30 days (**Taramasso, et al.,2019**).

The safety and performance of the TriCinch Coil System in symptomatic patients with moderate to severe TR (2+ to 4+) and annual diameter =40 mm confirmed by echocardiography will be further evaluated in two open label, single arm studies—the Early Feasibility Study of the Percutaneous 4Tech TriCinch Coil Tricuspid Valve Repair System and the Clinical Trial Evaluation of the Percutaneous 4Tech TriCinch Coil Tricuspid Valve Repair System (**NCT03632967,2019 and**

NCT03294200, 2019). The primary outcome measure in both studies will be 30-day all-cause mortality.

IRIS

The IRIS transcatheter annuloplasty ring (Millipede, Inc., Santa Rosa, CA, USA) is a complete semi-rigid ring that is placed in the supra-annular position and is then anchored and cinched thereby reducing the annular size and TR.

The IRIS implant consists of three components: a frame made of nitinol formed into a ring, anchors that engage the annular tissue, and collars that reduce the diameter of the frame to achieve proper valve leaflet coaptation. The IRIS has 2 distinct advantages—first, the ring is completely repositionable and adjustable prior to final deployment and second, the ring preserves the native anatomy without precluding future transcatheter options such as transcatheter edge-to-edge repair. A transcatheter delivery system for the tricuspid IRIS is currently under clinical development.

PASTA

Pledget-assisted suture tricuspid annuloplasty (PASTA) is a novel experimental transcatheter technique to create a double-orifice TV (**Khan, et al.,2018**). This technique is based on the Hetzer's double orifice suture technique, which has been performed in more than 90 patients with severe TR with no reoperation after 8.7 years (**Hetzer, et al.,2016**). In PASTA, pledgeted sutures are delivered via a transcatheter approach to appose septal and lateral targets on the TA, thereby reducing the TV orifice. In a preclinical animal study, PASTA successfully reduced annular and chamber dimensions and TR (**Khan, et al.,2018**). Four animals had procedure-related complications (leaflet tearing, chord entrapment, leaflet entrapment, transient AV node block, and ventricular fibrillation).

Transcatheter tricuspid valve intervention

MIA

The minimally invasive annuloplasty (MIA) device (Micro Interventional Devices, Inc., Newton, PA, USA) is a compliant, self-tensioning implant incorporating the company's proprietary PolyCor™ anchors and MyoLast™ thermoplastic elastomer that reduces TA dimension without sutures or other intervention. The safety and efficacy of the MIA device will be evaluated in 40 patients with functional TR in the Study of Transcatheter Tricuspid Annular Repair (STTAR) trial.

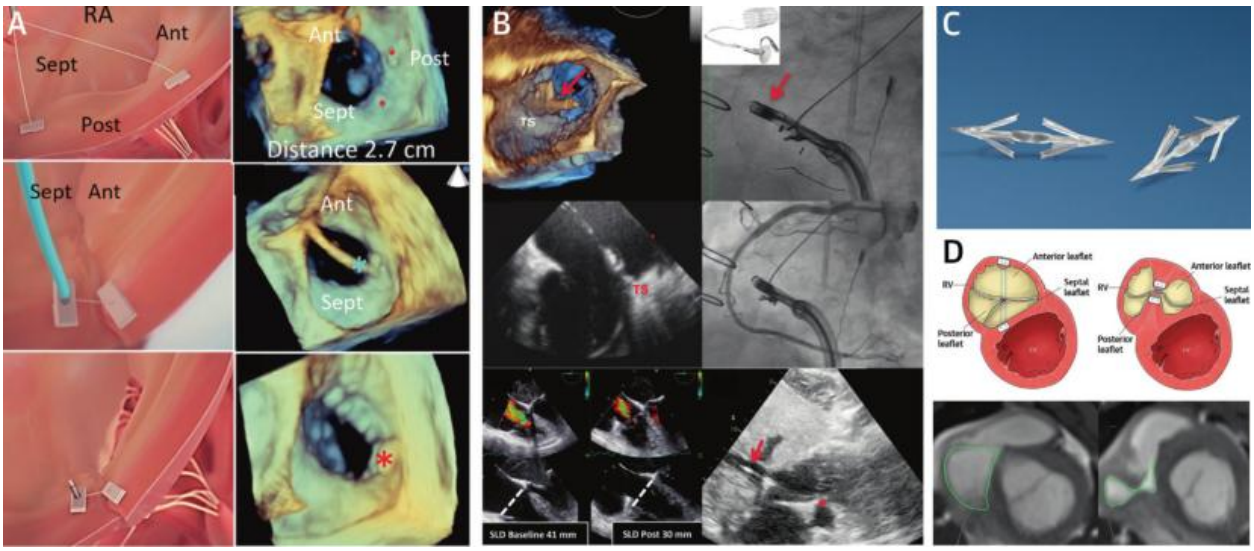
DaVingi™ TR system

The DaVingi™ TR system (Cardiac Implants LLC, Wilmington, DE, USA) is a transcatheter device designed to deliver an annuloplasty ring on the atrial side of the TV using right heart catheterization through the right internal jugular vein (**NCT03700918,2019**). The annuloplasty ring is a small multielement ring, consisting of an outer fabric layer, a pre-set stakes array, and an internal adjustment cord that can be adjusted at a later stage after the outer layer of the ring and stakes are encapsulated in new tissue growth. The safety and performance of the system will be evaluated in 15 patients with severe TR in the first in human study to assess safety and performance of the DaVingi™ TR system in the treatment of patients with functional TR (**NCT03700918,2019**).

TRAIPTA

Transatrial intrapericardial tricuspid annuloplasty (TRAIPTA) is a novel experimental TTVr system in which the right atrial appendage (RAA) is punctured from within to access the pericardium, which then allows a circumferential implant to be delivered along the AV groove within the pericardial space (**Rogers, et al., 2015**). The implant exerts compressive force over the TA. Tension on the implant can be adjusted to modify TA geometry and reduce TR. The RAA puncture is sealed using nitinol closure devices. In a preclinical animal study, TRAIPTA

reduced the tricuspid septolateral and anteroposterior dimensions, the annular area and perimeter, by 49%, 31%, 59%, and 24% (P<0.001), respectively (**Rogers, et al., 2015**). Small pericardial effusions were observed immediately post-procedure, but resolved completely at follow-up. In 4animals with functional TR, severity of TR by intracardiac echocardiography was reduced (**Rogers, et al., 2015**). This technique requires the pericardial space to be free of adhesions, thus precluding its use in patients with previous pericardiotomy or pericarditis.



Suture Annuloplasty Systems

(A) Trialign system. Illustration and 3-dimensional echocardiography during device deployment. Two suture pledgets are sequentially delivered at the anteroposterior

and septoposterior commissures and therefore plicated until maximal reduction in annular dimensions and regurgitant orifice is achieved. The blue asterisk indicates

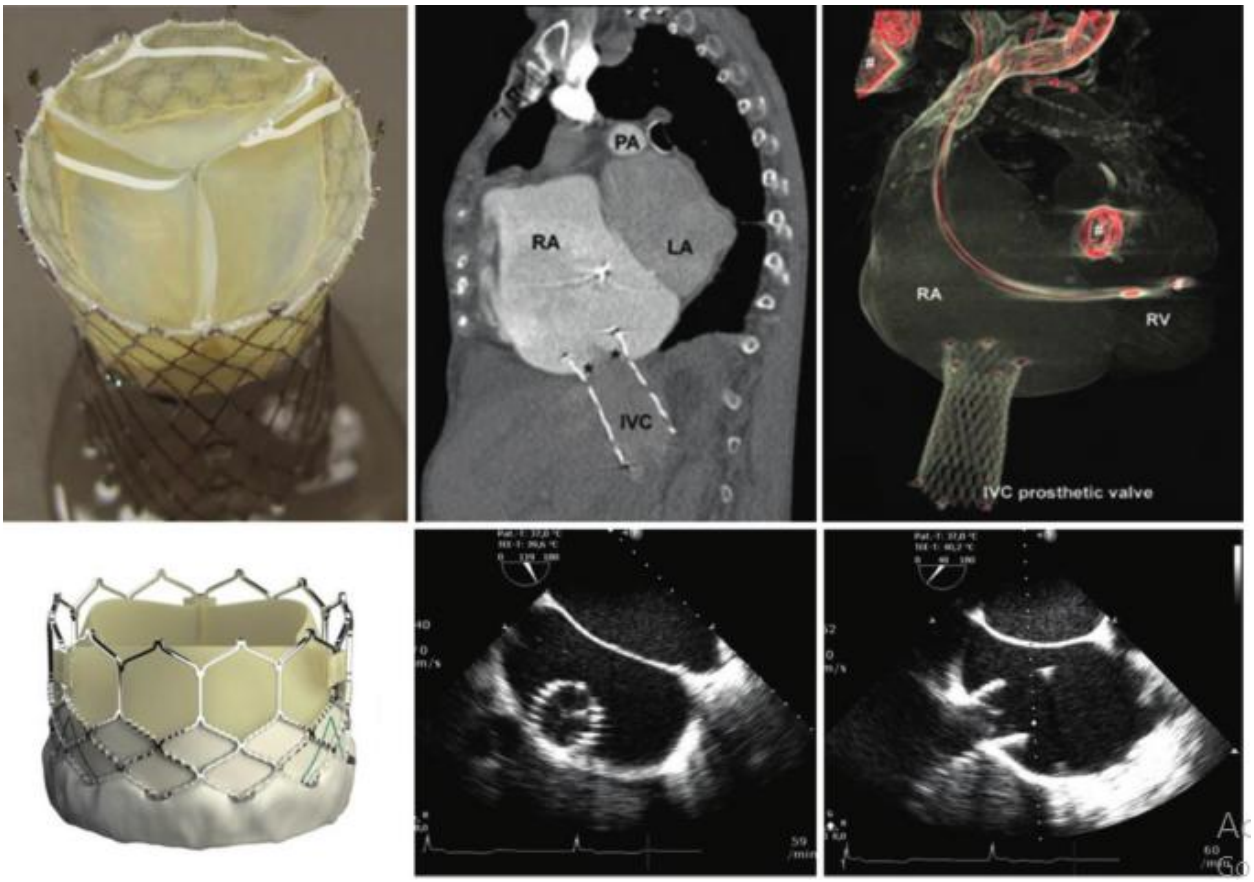
the wire delivery catheter; the red asterisk shows the Trialign device after deployment. Reprinted with permission from **Hahn et al. 2017**. (B) TriCinch. Transesophagealechocardiographic and fluoroscopic visualization of the device (red arrow) in the right atrium; right coronary angiography. Significant reduction of septolateral annulardiameter (SLD) post-cinching. Transthoracic subcostal view showing stent implanted in the inferior vena cava (small red arrow) and corkscrew implant at tricuspid annulus (asterisk). Reprinted with permission from Ancona et al. 2017. (C) Picture of MIA (minimally invasive annuloplasty technology), reprinted with permission from Micro Interventional Devices; investigational device only. (D) Pledget-assisted suture annuloplasty. Illustration and magnetic resonance images showing double-orifice valve creation by pledgeted sutures between the posteroseptal and mid-anterior annulus. Reprinted with permission from Khan et al.2018.

HETEROTOPIC CAVI

The objective of heterotopic CAVI, which does not specifically address the severity of TR per se, is to prevent caval backflow of TR and mitigate systemic venous congestion. Hemodynamic proof of pulsatile blood flow and caval backflow is required prior to heterotopic implantation. CAVI can be single (IVC only) or bicaval, depending on anatomic suitability. To date, 2 different devices have been used for CAVI: nondedicated balloon-expandable devices commonly used for transcatheter aortic valve replacement and dedicated self-expandable CAVI devices (TricValve, P&F Products Features Vertriebs, Vienna, Austria). Feasibility of heterotopic off-label use of the 29mm balloon-expandable SAPIEN valve (Edwards Lifesciences) was first reported by **Laule et al. 2013**. Because the IVC and SVC might dilate up to 35 and 40 mm, respectively, landing zone preparation and downsizing with caval pre-stenting or surgical banding are required. Because of the deploying mechanism and limited sizes of currently available valves (≤29 mm), balloon-expandable CAVI should preferably be restricted to IVC only (for IVC diameters ≤30 mm). Furthermore, considering the low-pressure system, lifelong anticoagulation is often required. The TricValve is a dedicated self-expandable pericardial valve mounted on a nitinol belly-shaped stent with little radial force, not requiring pre-stenting of the landing zone, specially designed for low-pressure circulation (Figure 8) (**Lauten, et al., 2014**). Implantation of the TricValve can be safely performed using a single- or dual-valve approach, with landing zone diameters #35 mm. The maximum available sizes are 8and 43 mm for the SVC and IVC, respectively. A multicenter registry including 25 patients treated by compassionate use with either the SAPIEN valve or the TricValve between 2010 and 2017 was recently reported (**Lauten, et al.,2018**). Single IVC valve implantation was performed in 19 patients (76%). Balloon expandable valves were mostly used in single valve procedures (16

of 19 [84%]), while self-expandable valves were most commonly used in double-valve procedures (5 of 6 [83%]). Procedural success was achieved in 92% of cases. In-hospital complications included 2 device embolizations requiring surgical removal. Significant improvements in NYHA class and in hemodynamic backflow (reduction of mean pressure in the IVC and right atrium) were observed, with no detrimental impact on cardiac index. Thirty day mortality was12% (3 of 25), with high 1-year mortality (14 of 22 [63%]) due mainly to high comorbid burden. Despite being the first transcatheter TV therapy used in humans (**Lauten, et al.,2011**), hemodynamic concerns following CAVI including the long-term impact of right atrial ventricularization, persistent right atrial volume overload, and increases in right ventricular afterload on right chamber function (although not confirmed in the latest experiences (**Lauten, et al.,2018 and Rakita, et al.,2017**) have perhaps prevented the broader use of CAVI for treating TR. Two ongoing trials are currently evaluating the feasibility of CAVI with the balloon expandable

SAPIEN valve for treating TR (Table 4).



The self-expandable TricValve and the Edwards SAPIEN balloon-expandable valve. Computed tomographic angiography, 3-dimensionalreconstruction, echocardiographic short- and long-axis views after device implantation. Reprinted with permission from Lauten et al. 2017.IVC=inferior vena cava; LA=left atrium; PA=pulmonary artery; RA=right atrium; RV=right ventricle.

TTVR

Since the first preclinical experience with a dedicated self-expandable bioprosthetic TV in 8 ewes reported in 2005 by **Boudjemline et al. 2005**, preclinical models with fully percutaneous TTVR platforms have been scarce (**Bai, et al., 2010**). The first case of TTVR in a human native TV was reported in 2014 by Kefer et al. 2014 using TA pre-stenting with 2 covered stents followed by nondedicated balloon-expandable SAPIEN valve implantation. However, the specific anatomic features of the TV have precluded expansion of the off-label use of these devices in the native TV.

NAVIGATE BIOPROSTHESIS. The NaviGate bioprosthesis (NaviGate Cardiac Structures, Lake Forest, California) is currently the only available dedicated device allowing fully orthotopic TTVR in humans. It consists of an atrioventricular valved stent and a delivery system. The Gate self-expanding tricuspid atrioventricular valved stent is a cone-shaped nitinol tapered stent with 3 xenogeneic pericardial leaflets, with a low (21-mm) height profile and annular winglets for secure anchoring of the TA and TV leaflets (Figures 7A to 7C). It is currently available in 5 different sizes: 36, 40-, 44-, 48-, and 52-mm. Slight oversizing of the device < 10% to the TA is generally recommended. The Gate system's delivery catheter is introduced through a 42-F introducer sheath via the transjugular vein (when venous access is ≥15 mm) or via the transatrial approach (right anterolateral mini-thoracotomy). Because of the long angulatory aspect of the current delivery system, sufficient space (~75 mm) is required to coaxially align and accommodate the capsule and the bar distal to the steering segment of the delivery catheter, from the SVC to the TA. The catheter shaft is 24-F and allows a 70o articulation to enable controlled valve release and secure valve engagement. Combination of aspirin and warfarin is the recommended antithrombotic regimen following valve implantation. The NaviGate valved stent was first evaluated in a swine model (**Navia, et al., 2018**). In this first preclinical experience, 12 healthy swine underwent NaviGate TTVR through both transjugular (n=6) and transatrial(n=6) approaches. All valves were successfully implanted, with 100% procedural success. All animals but 1 (which developed acute severe TR due to annulus-prosthesis mismatch with subsequent prosthesis migration into the right ventricle and death) survived the intervention. There was no obstruction of the right ventricular outflow tract, coronary arteries, or subvalvular apparatus. During follow-up (range: 30 to 210 days), no significant residual TR or increased transvalvular gradients were observed. The first-in-human successful implantations of the NaviGate bioprosthesis were performed by **Navia et**

al. 2017 in November 2016 and April 2017, in a severely dilated native TA and in a failed tricuspid annuloplasty ring, under transatrial and transjugular access, respectively. Initial data were first presented at 2017 Transcatheter Cardiovascular Therapeuticsmeeting (**Navia, 2017**). Since then, 11 compassionate-use cases have been performed worldwide, with a high procedural success rate and a low rate of significant procedure-related complications. All patients underwent fluoroscopy and transesophageal or intracardiac echocardiographic guidance. Marked improvements in TR severity were documented in all patients (prior 4 + TR in all patients, no postoperative paravalvular leak in 6 patients, trivial TR in 3 patients and mild TR in 2 patients). Significant reduction in central venous pressure was also observed (mean pre-operative and post-operative central venous pressures of 26.9- and 10.7-mm Hg, respectively). No patient developed tricuspid stenosis after the procedure (mean trans-tricuspid gradient 2.7 mm Hg). One patient required a permanent pacemaker implantation. Three patients died during follow-up (two after 1 week, one 6 months after), whereas the other 8 patients were alive at 3 weeks (n=4), 3 months (n=2), 6 months (n=1), and 9 months (n=1). Overall, this preliminary experience showed feasibility and safety of the NaviGate tricuspid valved stent, with 91%successful device implantation and good hemodynamic performance, with good prosthesis anchoring and sealing and low device-related complications. Modifications in a shortened distal angulation part of the delivery system are under current development in order to improve coaxiality with the TA and device sealing.

UPCOMING DEVICES FOR ORTHOTOPIC TTVR

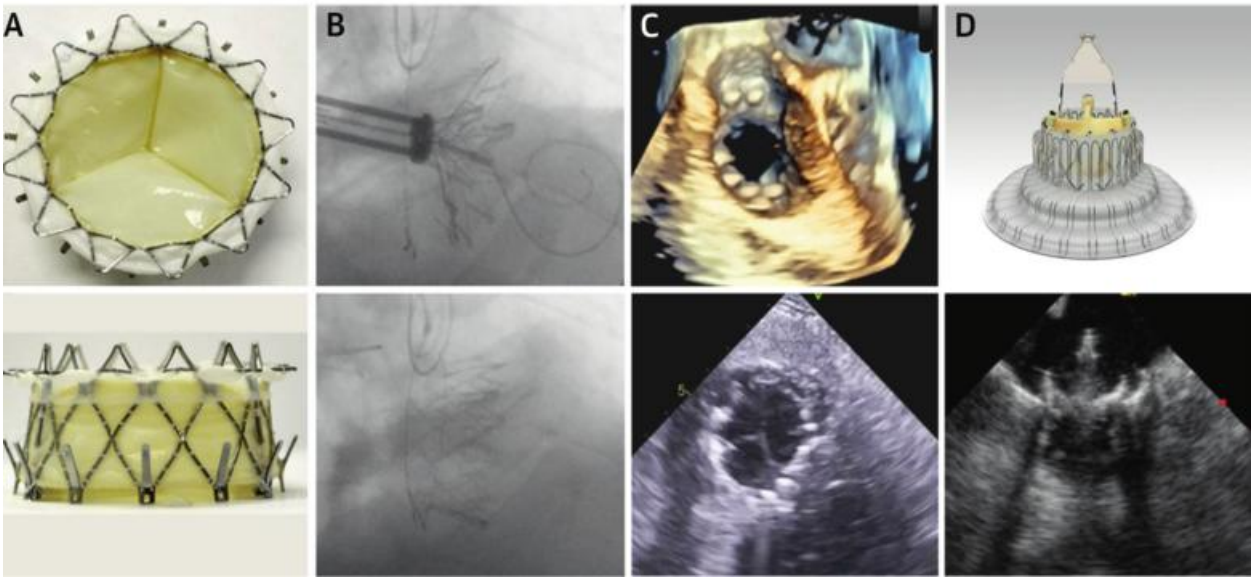
The LUX-Valve (Jenscare Biotechnology, Ningbo, China) is a self-expanding bovine pericardial tissue valve mounted on a nitinol stent frame and inserted transatrially through a minimally invasive thoracotomy. The device has a self-adaptive skirt to minimize paravalvular leak and a special anchoring mechanism for secure anchoring within the right ventricle. Initial experimental data in a chronic

goat model were recently reported, with promising results at 6 months (Figure 9D) (Lu,2017). Further studies assessing the safety and long-term efficacy of this and other emerging orthotopic TTVR devices (TRiCares, Aschheim, Germany) are warranted.

CLINICAL PERSPECTIVES ON TRANSCATHETER TRICUSPID THERAPY

Most patients enrolled in the early clinical experiences with transcatheter tricuspid therapies were at high or prohibitive surgical risk, treated under compassionate or feasibility clinical programs. Most patients undergoing TTVr or
TTVR were high-risk patients (mean European System for Cardiac Operative Risk Evaluation II score 9), predominantly women (60%), past the seventh decade of life. As anticipated, the chief mechanism of TR was functional in 96% of these patients, due mostly to right ventricular dysfunction, tricuspid annular dilatation, and impaired leaflet coaptation, probably exacerbated by a high prevalence (85%) of atrial fibrillation. One-half of patients had undergone a prior open-heart surgery, and one quarter of patients (up to one-third among MitraClip and CAVI recipients) had prior permanent transtricuspid leads, which did not preclude procedural success among those devices specifically targeting leaflet coaptation (Perlman, et al. 2017). Interestingly, recent experiences have shown the feasibility of TTVr in patients with pacemaker leads using annuloplasty systems, such as the Cardioband and Trialign devices (**Nickenig, 2017,and Meduri,2017**).

Transcatheter tricuspid valve intervention



(A to C) The NaviGate valve. (A) Inflow and lateral views. (B) Fluoroscopy: transatrial tricuspid valved stent. (C) Three-dimensional and 2-dimensional echocardiography.(D) The LUX-Valve, Courtesy of Dr. Fang-Lin Lu, Changhai Hospital (Shanghai, China).

DEVICE SELECTION.

Accurate diagnosis of the underlying anatomy and pathophysiology is essential when assessing different available transcatheter tricuspid therapies. To date, coaptation devices have been the most commonly used technologies (>50%), particularly interventional edge-to-edge repair in up to 40% of cases, followed by annuloplasty systems (30%). Specific anatomic features from the TV complex might vary according to the causing mechanism (primary vs. secondary) and throughout the progressive stages of ventricular remodeling in patients with functional TR. Thus, individual patient-specific device selection is paramount to be ultimately successful. Primary TR accounts for ~10% of cases of TR and can be due to congenital (Ebstein's anomaly,prolapse) or acquired diseases (rheumatic, endocarditis, carcinoid, endomyocardial fibrosis, intracardiac leads, or bioptome-related iatrogenic trauma).Although the inclusion of patients with primary TR has been anecdotal in the early clinical experience with transcatheter TV technologies, some selected patients deemed at too high risk for standard TV

surgery could still benefit from lesser invasive alternatives. The use of MitraClip might be suitable for cases of leaflet prolapse. In patients with lead-induced TR, coaptation devices may be prioritized, whereas TTVR could be considered for patients with intracardiac leads and extreme tricuspid annular dilation, as well as for rheumatic TR. Secondary TR has been divided into 3 stages for therapeutic purposes (**Raja and Dreyfu, 2010**). In the early stage, initial dilation of the right ventricle leads to tricuspid annular dilation without significant leaflet tethering. Annular-based systems should easily repair TR in these first stages. In the absence of long-term durability data for transcatheter TV therapy and on the basis of a surgical predicate, ring may be preferred over suture annuloplasty when possible in order to reduce TR recurrence (**Navia, et al., 2010**). In the second stage, progressive right ventricular and tricuspid annular dilation develop, impairing leaflet coaptation. The likelihood for successful TTVr using annuloplasty alone is less suitable in cases with progressive tethering and tricuspid annular dilation. In such cases, coaptation devices or combination of different approaches (e.g., combined edge-to-edge repair and annuloplasty, or Trialign with Cardio- band) may lead to more pronounced TR reduction (**Taramasso, et al., 2017**). Interestingly, the use of the NaviGate bioprosthesis in these intermediate stages could result in complete TR elimination, preventing further disease progression, which may exert a positive impact on functional status and on survival over time. Finally, as the right ventricle continues to remodel, further leaflet tethering worsens, resulting in a lack of coaptation and massive or torrential TR. When severe tethering occurs, any repair attempt could be considered futile, and TTVR should be preferred over TTVr (**Buzzatti, et al., 2018**). Orthotopic TTVR should be first considered for patients with preserved or mild to moderate right ventricular dysfunction. In more advanced stages of chronic heart failure, comprehensive estimation of clinical benefit is paramount to prevent potential

TTVR-related futility, and medical treatment should be considered, contemplating the possibility of compassionate TTVR or CAVI for carefully selected patients.

DRAWBACKS AND FUTURE DIRECTIONS.

Standardized imaging for transcatheter tricuspid interventions. Because of the heterogeneity and complex nature of the TV disease, comprehensive imaging assessment of the right ventricle and TV is essential to achieve optimal and lasting procedural results. Limitations and lack of consistency among current echocardiographic parameters along with notable discrepancies between marked clinical improvements in symptoms and QoL and modest reductions in TR severity in most TTVr and TTVR studies conducted to date, underscore a compelling need for novel quantification methods for assessing TR severity in this unusual population.

Extending the grading scheme beyond severe TR, including massive and torrential TR (**Hahn and Zamorano, 2017**), or considering a threshold percentage reduction of quantification parameters above severe (e.g., 25% reduction in vena contracta or effective regurgitant orifice area) may help better identify those patients with significant clinical benefit after TV interventions. Besides, given the complex anatomy of both the TA and right ventricle, an increasing role of alternative imaging techniques such as cardiac magnetic resonance, CT imaging, and intracardiac echocardiography ought to be expected in the coming years.

Further studies are needed to determine the exact role of these novel imaging technologies in this field.

Durability and long-term outcomes

Durability remains the Achilles heel of most surgical interventions addressing the TV. Many factors, such as right ventricular remodeling and dysfunction,

tricuspid annular size progression, and pulmonary hypertension, may contribute to the high rates of TR recurrence observed following surgical TR correction. Surgical experience has shown more sustained durability of ring annuloplasty compared with suture annuloplasty (**Navia, et al., 2010**)., as well as for TV replacement over repair. However, concerns about increased perioperative mortality for TV replacement compared with repair in contemporary series—somewhat linked to selection bias of patients with larger tricuspid annular dilation and more severe right ventricular dysfunction—have led to a trend over time toward TV repair rather than replacement (**Zack, et al., 2017**). To date, no long-term durability data exist for transcatheter TV interventions. However, it is anticipated that TTVr and TTVR will need to overcome the same barriers as their surgical counterparts, because most of these percutaneous devices replicate open surgical techniques. Because of the very early experience of transcatheter tricuspid technologies, long-term clinical and echocardiographic data for TTVr and TTVR are currently lacking and therefore will need to be carefully evaluated in coming trials.

Antithrombotic therapy.

Optimal antithrombotic therapy following transcatheter TV interventions remains a controversial issue. Notably, nearly 90%of patients treated with percutaneous TV devices to date presented with pre-existing atrial fibrillation, thus necessitating underlying systemic anticoagulation. However, in the absence of atrial fibrillation, the best post-procedural antithrombotic therapy remains unclear. Current guidelines recommend 3 months of oral anticoagulation after surgical TV repair or replacement (**Kim, et al., 2009**). Despite the very low rate of device thrombosis following transcatheter TV procedures (a single Forma device thrombosis in the setting of subtherapeutic anticoagulation), anticoagulation

therapy for the initial months following TTVr or TTVR is advisable, considering that the implantation of these devices occurs in right-sided low-pressure circulation regions of the heart more prone to thrombosis.

Larger studies with longer-term follow-up are warranted to determine the real incidence of device related thrombosis, as well as to elucidate the optimal post-procedural antithrombotic therapy in this population.

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