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Valvular Heart Disease (J Dal-Bianco, Section Editor)

Transcatheter Tricuspid Valve Therapy

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Abstract

Purpose of review Despite the increasing prevalence of tricuspid regurgitation (TR) and its association with poor survival, isolated tricuspid valve (TV) surgery remains infrequent. To address this unmet clinical need, several less invasive transcatheter TV therapies have emerged as an alternative to surgery in high-risk patients with severe functional TR. The objective of this review is to summarize the current progress and future directions in the field of transcatheter TV therapies.
Recent findings Transcatheter TV repair devices are aimed at improving leaflet coaptation either directly by bringing the leaflets together or indirectly by addressing the dilated annulus. Transcatheter TV replacement, on the other hand, can be orthotopic (implantation of prosthetic valve in an anatomically correct position in the tricuspid annulus) or heterotopic (implantation of prosthetic valve in a different anatomic location to counter the hemodynamic and clinical consequences of severe TR). Data from first-in-man and phase 1/2 clinical studies on the safety and efficacy of various transcatheter TV therapies appear promising.
Summary Technological advancement and increased experience are anticipated to improve outcomes of transcatheter TV therapy in the coming years. Ongoing and future studies should focus on careful patient selection, optimal timing of intervention, and long-term clinical outcomes and device durability.

Introduction

Tricuspid regurgitation (TR) is a common valvular heart disease, which affects > 1.6 million people in the United States (US) and > 70 million people worldwide [1, 2]. The age- and sex-adjusted prevalence of ≥ moderate TR in the US is estimated to be 0.55% [3]. The prevalence of TR increases with age

and is significantly higher in women. With the projected increase in the number of people ≥ 65 years of age in the US and worldwide, the prevalence of TR is likely to increase dramatically in the near future. Although the majority of patients have trivial or mild TR, increasing severity of TR is associated with increasing 1-year mortality [4]. Despite the rising prevalence of TR and its association with poor survival, the majority of patients are managed medically in the absence of another indication for cardiac surgery, and only 0.5% undergo tricuspid valve (TV) repair or replacement [5]. Isolated TV surgery accounts for only 20% of TV interventions and is rarely performed due to an in-hospital mortality of 2 to 10% and a paucity of data demonstrating improved survival [6–8]. Hence, there is an unmet clinical need for novel surgical or percutaneous therapies for TR. In this article, we will review the current progress and future directions in the field of transcatheter tricuspid valve therapies.

Tricuspid valve anatomy and pathophysiology of TR

The TV is a complex structure consisting of 3 leaflets (anterior, posterior, and septal) arising from the tricuspid annulus and attached via chordae tendineae to the papillary muscles of the right ventricle (RV) [9]. The TV annulus is a nonplanar structure (the posteroseptal portion is more ventricular and the anteroseptal portion is more atrial) with a more flattened oval shape than the saddle-shaped mitral annulus. It is also a dynamic structure that varies in shape and size throughout the cardiac cycle and with loading conditions. The TV orifice is larger and more triangular than the mitral valve. Table 1 summarizes the anatomical aspects that can represent a challenge for the transcatheter treatment of TR [9].

Table 1. Anatomical challenges of transcatheter tricuspid valve therapy

Tricuspid annulus
• Large size
• Nonplanar and elliptical shape
• Noncalcified
• Dynamic structure
Right ventricle
• Thin free wall
• Trabeculae, muscular bands, and chordae tendineae
• Acute increase in RV afterload following TV repair/replacement
• Risk of right ventricular outflow tract obstruction
• Slow flow in right ventricle
Surrounding structures
• Proximity of AV node and His bundle
• Proximity of right coronary artery to annulus
• Risk of coronary sinus or vena cava occlusion
Pre-existing pacemaker/defibrillator leads

Approximately 90% of TR in adults is functional (secondary) due to annular dilation and leaflet tethering resulting in leaflet tip malcoaptation. Thus, transcatheter TV repair devices are aimed at improving leaflet coaptation either directly by bringing the leaflet tips together or indirectly by addressing the dilated annulus (Fig. 1). Transcatheter TV replacement, on the other hand, can be orthotopic (implantation of prosthetic valve in an anatomically correct position in the tricuspid annulus) or heterotopic (implantation of prosthetic valve in a different anatomic location to counter the hemodynamic and clinical consequences of severe TR and RV dysfunction).

Transcatheter tricuspid valve repair

Leaflet/coaptation devices

MitraClip

The off-label use of the MitraClip system (Abbott Vascular, Santa Clara, CA) is the most commonly performed transcatheter TV repair procedure, either for isolated severe TR or combined severe TR and severe mitral regurgitation (MR) [10••]. The MitraClip device is a cobalt-chromium polyester-covered implant with 2 arms that are opened and closed by control mechanisms on the clip delivery system. The clip may be repositioned or removed prior to final deployment, and additional devices can be implanted to achieve adequate TR reduction. Two techniques to achieve reduction of TR with the MitraClip system have been described—a triple-orifice technique (TOT), where clips are placed centrally between the septal and anterior tricuspid leaflet as well as the septal and posterior tricuspid leaflet, and a bicuspidization technique (BT), where clips are placed between the septal and anterior tricuspid leaflet [11]. Both techniques have been shown to achieve comparable results, although the bicuspidization technique is considered more technically feasible and is more frequently performed [11].

Several single-center studies and multicenter registries of patients with severe TR treated with transcatheter edge-to-edge repair using the MitraClip system have demonstrated acute procedural success rates of > 90%, with procedural success defined as a 1-grade improvement in TR severity. Significant improvement in NYHA functional class, 6-min walk distance (6MWD), and quality of life (QoL) up to 1 year have been associated with the modest improvement in TR severity [10••, 12–14]. Thirty-day, 6-month, and 12-month mortality rates in various studies were 2.8%, 16%, and 37.5%, respectively [10••, 13, 14]. The Trial to Evaluate Treatment With Abbott Transcatheter Clip Repair System in Patients With Moderate or Greater Tricuspid Regurgitation (TRILUMINATE) is an ongoing prospective, single-arm, multicenter study to evaluate the safety and effectiveness of the tricuspid valve repair system (Abbott Vascular, Santa Clara, CA) for treating symptomatic ≥ 2+ TR in patients currently on medical management and who are deemed appropriate for percutaneous transcatheter intervention [15].

PASCAL

The first-in-man compassionate use of the Edwards PASCAL transcatheter mitral valve repair system (Edwards Lifesciences, Irvine, CA, USA) in 23

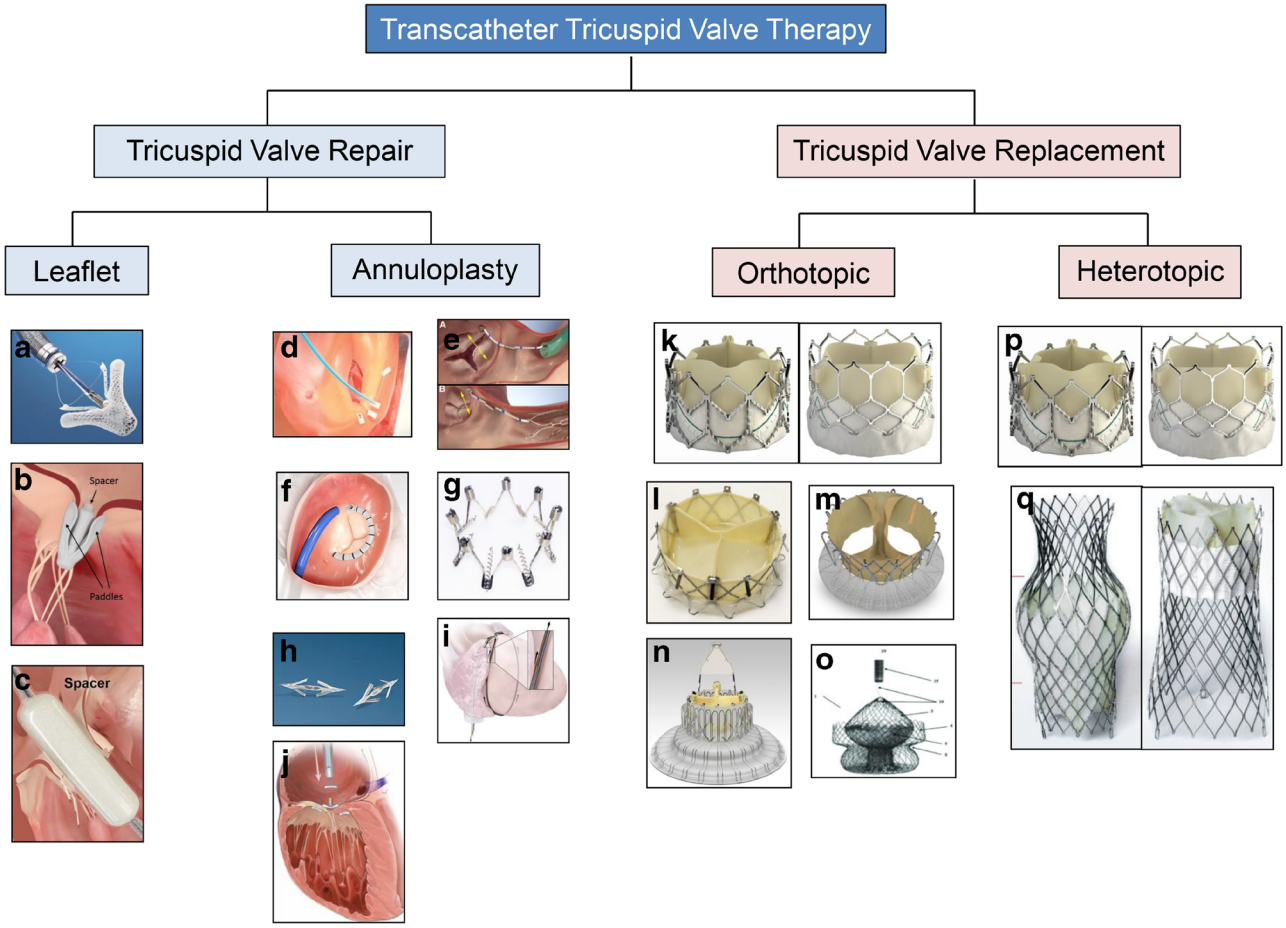

Fig. 1. Transcatheter tricuspid valve therapies. Transcatheter tricuspid valve repair (**a**–**j**) and replacement (**k**–**q**) therapies currently in use or under development. (**a**) MitraClip, (**b**) PASCAL, (**c**) FORMA, (**d**) Trialign, (**e**) TriCinch, (**f**) Cardioband, (**g**) Iris, (**h**) Minimally Invasive Annuloplasty (MIA) device, (**i**) transatrial intrapericardial tricuspid annuloplasty (TRAIPTA), (**j**) pledget-assisted suture tricuspid annuloplasty (PASTA), (**k**) and (**p**) SAPIEN XT/SAPIEN 3 valves, (**l**) GATE tricuspid valve stent, (**m**) Trisol valve, (**n**) LUX-Valve, (**o**) TriCares valve, (**q**) TricValve (superior and inferior cava valves).

patients with severe MR has been previously reported [16]. The PASCAL system consists of a 10-mm central spacer that acts as filler in the regurgitant orifice of the valve and is attached to the valve leaflets by two paddles and clasps. The spring-loaded paddles (25 mm width in grasping position) and clasps (10 mm length) are wide and allow uniform distribution of load across the surface area of the inserted leaflets. The convex curvature of the tip of the paddles reduces tension on the valve leaflets [16].

Fam et al. [17] recently reported a case of an 82-year-old woman with torrential TR and NYHA functional class IV dyspnea, severe fatigue, ascites, and peripheral edema, who underwent successful transcatheter edge-to-edge TV repair using the PASCAL system with reduction of TR to mild, improvement in NYHA functional class to II, resolution of ascites, and

improvement in QoL and 6MWD at 1 month. However, further research to assess the durability, safety, and effectiveness of this system is needed.

FORMA

The FORMA system (Edwards Lifesciences, Irvine, CA) is a spacer device (42 mm length) placed within the TV over a rail that is anchored into the RV myocardium [18]. The spacer passively expands via holes within the spacer shaft and acts as a surface for valve leaflet coaptation, thereby reducing the effective regurgitant orifice area (EROA). Two coaptation diameter sizes (12 mm and 15 mm) are currently available. The 1-year clinical and echocardiographic outcomes of the first-in-human, multicenter, compassionate use experience with the FORMA system has been reported [19•]. At 1 year, there were no deaths, significant arrhythmias, device infections, or dislocations. Device thrombosis occurred in 1 out of 15 (7%) patients at 1 year. Among the 14 patients with successful device implantation and 1-year follow-up, 79% were in NYHA functional class I/II ($p < 0.001$), the average 6MWD increased by 84 m ($p = 0.03$), and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score improved by 18 points ($p = 0.02$) compared with baseline. Echocardiography showed a reduction in TR to moderate-severe or less in 69% of patients by 30 days ($p = 0.001$) and 46% by 1 year ($p = 0.01$) [19•].

Two studies are currently ongoing to better understand the safety and efficacy of the FORMA system—the Early Feasibility Study of the Edwards FORMA Tricuspid Transcatheter Repair System, which will enroll 60 participants with the primary outcome measure of procedural success (defined as device success and freedom from device or procedure-related severe adverse events) at 30 days, and the Repair of Tricuspid Valve Regurgitation Using the Edwards TricuSPid TrAnsCatheter REpaiR System (SPACER) trial, which will enroll 78 participants and examine the primary endpoint of cardiac mortality of the as-treated cohort at 30 days compared with a literature-derived performance goal based on high-risk surgical outcomes for TV repair/replacement [20, 21].

Annuloplasty devices

Trialign

The Trialign device (Mitralign Inc., Tewksbury, MA) is a transcatheter suture-based tricuspid annuloplasty system that reduces tricuspid annular diameter through tissue plication [22]. The Trialign system 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 [23, 24]. Two pledgets are positioned at the anteroposterior and septoposterior commissure and then sutured together using the dedicated plication lock device, thus plicating the posterior leaflet. A distance of 25–28 mm between the pledget in the anteroposterior and septoposterior location is recommended [25]. A second pair of pledgets can be implanted in cases of suboptimal results to obtain a consistent reduction in annular dimensions.

The Percutaneous Tricuspid Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation (SCOUT) trial was a prospective, single-arm, multicenter study that tested the feasibility and safety of the Trialign system in 15 patients with NYHA functional class ≥ II and moderate or greater functional TR [26•]. Technical success rate at 30 days was 80%. Three single-pledget annular detachments occurred but did not necessitate reintervention. In the remaining 12 patients, the Trialign system resulted in significant reductions in tricuspid annular diameter and EROA, with significant increase in left ventricular stroke volume (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 m to 298.0 ± 107.6 m; $p = 0.008$) [26•]. The ongoing Safety and Performance of the Trialign Percutaneous Tricuspid Valve Annuloplasty System (PTVAS) for Symptomatic Chronic Functional Tricuspid Regurgitation (SCOUT-II) is a prospective, single-arm, multicenter, open-label study that will enroll up to 60 patients from up to 15 sites in Europe and US [27]. The primary endpoint is 30-day all-cause mortality.

TriCinch

The TriCinch system (4Tech Cardio Ltd., Galway, Ireland) attempts to reproduce the Kay procedure by cinching at the anteroposterior commissure, thus reducing septolateral dimensions [28]. The TriCinch system comprises two components: (1) a stainless steel corkscrew implant, to be placed in the anterior tricuspid annulus, in proximity to the anteroposterior commissure; and (2) a self-expanding nitinol stent that is deployed below the hepatic region of the inferior vena cava [29]. The first-in-man feasibility study, Percutaneous Treatment of Tricuspid Valve Regurgitation With the TriCinch System™ (PREVENT), has completed enrollment ($n = 24$) and will provide important data on the safety and efficacy of this device [30]. Data from the TriValve Registry on 14 patients who underwent TV repair with the TriCinch system showed procedural success rate of 62.5% and zero deaths at 30 days [10••].

Cardioband

The Cardioband (Edwards Lifesciences, Irvine, CA) is a polyester sleeve with radiopaque markers spaced 8 mm apart containing a pre-mounted contraction wire connected to an adjusting spool [31]. Twelve to 17 anchors are implanted through the sleeve. Once the last anchor is delivered, a size adjustment tool is inserted, and the implant is then contracted. The 1-year outcomes of transcatheter mitral valve repair for functional MR using the Cardioband system were recently reported [31]. The Cardioband has been implanted under compassionate use in 5 patients with functional TR with satisfactory results (23 to 45% reduction of the tricuspid annular diameter and 50 to 70% reduction of the EROA without any procedure-related serious adverse events) [28].

The Cardioband system received Conformité Européenne (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 [32, 33]. Successful access, deployment, and positioning of the Cardioband

device occurred in 100% of patients. Major serious adverse events at 30 days included death ($n = 2$), stroke ($n = 1$), and major bleeding complications ($n = 3$). The Cardioband system resulted in 17% reduction in septolateral diameter ($p < 0.01$), 50% reduction in EROA ($p < 0.001$), 31% reduction in vena contracta ($p < 0.001$), and 7% reduction in LVSV ($p = 0.06$), as well as significant improvement in NYHA functional class, KCCQ score, and 6MWD at 30 days [33]. The US Edwards Cardioband Tricuspid Valve Reconstruction System Early Feasibility Study is currently ongoing [34].

IRIS

The IRIS transcatheter annuloplasty ring (Millipede, Inc., Santa Rosa, CA) 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 valvular regurgitation. The ring is completely repositionable and adjustable prior to final deployment and preserves the native anatomy without precluding future percutaneous options such as transcatheter edge-to-edge repair. 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 early experience included 7 patients with severe functional MR who underwent surgical ($n = 4$) or transcatheter ($n = 3$) implantation of the IRIS mitral annuloplasty ring [35]. A transcatheter delivery system for the tricuspid IRIS is currently under clinical development.

MIA

The Minimally Invasive Annuloplasty (MIA) device (Micro Interventional Devices, Inc., Newton, PA) reduces tricuspid annular dimension without sutures or other intervention due to the compliant, self-tensioning MIA implant incorporating the company's proprietary PolyCor™ anchors and MyoLast™ thermoplastic elastomer. The Study of Transcatheter Tricuspid Annular Repair (STTAR) trial will evaluate the safety and efficacy of the MIA device in 40 patients with functional TR [36].

TRAIPTA

Transatrial intrapericardial tricuspid annuloplasty (TRAIPTA) is a novel experimental transcatheter TV repair system in which the pericardium is accessed via a puncture of the right atrial appendage (RAA) from within, and a circumferential implant is delivered along the atrioventricular groove within the pericardial space [37]. The implant exerts compressive force over the tricuspid annulus and tension on the implant can be adjusted to modify tricuspid annular geometry and reduce TR. The RAA puncture is sealed using nitinol closure devices. In a preclinical animal study, tricuspid septal-lateral and anteroposterior dimensions, the annular area, and perimeter, were reduced by 49%, 31%, 59%, and 24% ($p < 0.001$), respectively [37]. Small pericardial effusions were observed immediately post-procedure, but resolved completely at follow-up. In 4 animals with functional TR, severity of TR by intracardiac echocardiography was reduced [37]. The main limitation of this technique is that

TRAIPTA requires the pericardial space to be free of adhesions, thus precluding its use in patients with previous pericardiotomy or pericarditis.

PASTA

Pledget-assisted suture tricuspid annuloplasty (PASTA) is a novel experimental percutaneous technique to create a double-orifice TV [38]. This technique is based on 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 [39]. PASTA reduces the TV orifice by apposing septal and lateral targets on the tricuspid annulus using percutaneously delivered pledgeted sutures. In a preclinical study in pigs, PASTA successfully reduced annular and chamber dimensions and TR [38]. Four animals had procedure-related complications including leaflet tearing, chord entrapment, leaflet entrapment, transient AV node block, and ventricular fibrillation.

Transcatheter tricuspid valve replacement (TTVR)

Orthotopic tricuspid valve replacement

Valve-in-valve or valve-in-ring

Several investigators have demonstrated the use of currently available transcatheter aortic valve (SAPIEN/SAPIEN XT/SAPIEN 3, Edwards Lifesciences, Irvine, CA) or transcatheter pulmonary valve (Melody™, Medtronic Inc., Minneapolis, MN) prosthesis for valve-in-valve (ViV) or valve-in-ring (ViR) application in patients with degenerated surgical bioprosthetic TV or surgical tricuspid ring repair [40, 41••]. Mid-term outcomes of the largest cohort of patients from the Valve-in-Valve International Database (VIVD) Registry who underwent transcatheter tricuspid ViV or ViR were recently reported [41••]. From 2008 through 2017, 306 patients underwent TTVR (284 ViV and 22 ViR) with a Melody valve (138 [45%]) or a SAPIEN valve (168 [55%]; SAPIEN in 19, SAPIEN XT in 82, and SAPIEN 3 in 67). Median follow-up duration was 15.9 months. Freedom from death, TV reintervention, or valve-related events at 3 years occurred in 64% of patients. The cumulative 3-year incidence of death, reintervention, and valve-related adverse outcomes (endocarditis, thrombosis, or significant dysfunction) was 17%, 12%, and 8%, respectively. The annualized incidence rate of endocarditis was 1.5% per patient-year (95% CI 0.45 to 2.5%). There was no difference in valve-related outcomes according to TTVR valve type [41••].

GATE™

The GATE™ tricuspid valved stent (NaviGate Cardiac Structures, Inc., Lake Forest, CA) system consists of an atrioventricular valved stent, a delivery system, a compression loading system, and an introducer sheath [42]. The valve stent is nitinol alloy with a conical shape and is available in 5 different sizes (36, 40, 44, 48, and 52 mm diameter). Slight oversizing of the device < 10% to the tricuspid annulus is generally recommended.

Twelve RV tines grasp the tricuspid leaflets from the RV side. There are 12 right atrial (RA) winglets perpendicular to the conical stent and covered by a microfiber polyester cloth designed to provide a seal. The 3 leaflets and the skirt are made of treated equine pericardium. The delivery system consists of a tip-deflecting catheter designed to go through a 42 F introducer sheath. The first-in-human successful implantation of the GATE valved stent was performed by Navia et al. [43] in 2 patients—one with a severely dilated tricuspid annulus and one with a failed tricuspid annuloplasty ring. Since then, single-center experiences with the GATE system have been reported from the US and Switzerland in 5 and 4 patients, respectively [42, 44]. Both studies reported significant reduction in TR and improvement in cardiac output following valve implantation.

Trisol

The Trisol valve (TriSol Medical, Yokneam, Israel) is constructed out of nitinol frame with specially designed sail-like leaflet, which allows augmented RV closing volume and pressure relief [45, 46]. A single bovine pericardial piece is attached to the nitinol frame in two opposite central commissures, and functions as two separate leaflets. The leaflets move to the center of the lumen during diastole, creating two large lumens for diastolic filling of the RV. During systole, the two leaflets close and coapt to the full circumference of the tricuspid annulus in a dome shape structure that increases the RV closing volume to about 20 mL. This increased closing volume is expected to prevent the acute surge in afterload, and to better accommodate the concomitant RV dysfunction. The valve is currently in the preclinical stage.

LUX-Valve

The LUX-Valve (Jenscare Biotechnology, Ningbo, China) is a bovine pericardial tissue valve mounted on a self-expandable nitinol stent covered by a layer of polyethylene terephthalate (PET) [47]. The D-shaped repositionable prosthesis is inserted through the right atrium via a minimally invasive thoracotomy at the 3rd or 4th anterolateral intercostals. The feasibility of this novel TTVR device was demonstrated in a preclinical animal study; however, the first-in-man study is still awaited [47].

TriCares

The TriCares (TRiCares GmbH, München, Germany) valve is a self-expanding prosthesis made from bovine pericardial tissue mounted on a nitinol stent frame [1]. The valve is currently in the preclinical stage.

Heterotopic caval valve implantation

Compared with orthotopic TTVR, heterotopic caval valve implantation (CAVI) has the following advantages: (1) the implantation technique is less complex, (2) the introduction of foreign material in the RV inflow tract is avoided potentially resulting in lower risk of injury to ventricular structures, and (3) the device does not interfere with pre-existing transtricuspid pacemaker or defibrillator leads. The first-in-man CAVI was

performed by Lauten et al. [48] in 2010 using a custom-made self-expanding heart valve implanted into the inferior vena cava (IVC). The device was anchored in the IVC at the cavoatrial junction with the level of the valve aligned immediately above the hepatic inflow and protruding into the RA. After deployment, excellent valve function was observed resulting in a marked reduction in caval pressure and an abolition of the ventricular wave in the IVC. Within the first 8 weeks after implantation, the patient experienced gradual improvement of symptoms related to venous congestion and right heart failure.

From March 2010 through February 2017, 25 patients have now undergone heterotopic CAVI in Europe under a compassionate clinical use program using balloon-expandable SAPIEN XT/SAPIEN 3 valves (Edwards Lifesciences, Irvine, CA; $n = 17$), self-expandable TricValve (P&F, Vienna, Austria; $n = 7$) or Direct Flow Medical valve prosthesis (Direct Flow Medical, Inc., Santa Rosa, CA; $n = 1$) [49]. The TricValve is designed as a set of 2 self-expandable valves specifically for SVC and IVC implantation in the low pressure circulation [50]. The SVC valve is a belly-shaped tapered device for anchoring in dilated, tapered SVC configuration. The IVC valve is deployed at the level of the diaphragm and protruding into the RA. Both devices are made of bovine pericardium, and the inner part of the atrial stent portion is lined with a PTFE skirt. The Direct Flow Medical valve prosthesis is no longer available after the company stopped operating in December 2016. Of the 25 patients, 19 (76.0%) underwent IVC-only implantation and 6 (24.0%) underwent BiCAVI (IVC and SVC) [49]. Procedural success was achieved in 96% of patients. Early and late valve migration requiring surgical intervention occurred in 1 patient each. Thirty-day and in-hospital mortality were 12% and 24%, respectively. Two ongoing studies, Heterotopic Implantation Of the Edwards-Sapien Transcatheter Aortic Valve in the Inferior VEna Cava for the Treatment of Severe Tricuspid Regurgitation (HOVER) and Treatment of Severe Secondary TRIcuspid Regurgitation in Patients With Advance Heart Failure With CAval Vein Implantation of the Edwards Sapien XT VALve (TRICAVAL), will provide further evidence on the safety and efficacy of heterotopic implantation of the Edwards SAPIEN XT valve in the IVC for the treatment of severe TR in patients who are inoperable or at a very high surgical risk for TV replacement [51, 52].

Summary

Despite the increasing prevalence of TR and its association with poor survival, the majority of patients are managed medically in the absence of another indication for cardiac surgery, and only 0.5% undergo TV repair or replacement. To address this unmet clinical need, several less invasive transcatheter TV therapies have emerged as an alternative to surgery in high-risk patients with severe functional TR. Although this field is still in its infancy, the initial data on the safety and efficacy of various transcatheter TV therapies appears promising. Technological advancement, device innovation, and increased experience in this field are anticipated to improve procedural and clinical outcomes in the coming years.

Ongoing and future studies should focus on careful patient selection, optimal timing of intervention, standardized TR grading schemes, and long-term clinical outcomes and device durability.

Compliance with Ethical Standards

Conflict of Interest

Dhaval Kolte declares no potential conflicts of interest. Sammy Elmariah reports a grant from Edwards Lifesciences and personal fees from AstraZeneca and Medtronic.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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