

## THE PRESENT AND FUTURE

### JACC STATE-OF-THE-ART REVIEW

# Transcatheter Tricuspid Valve Interventions



## Landscape, Challenges, and Future Directions

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### ABSTRACT

Tricuspid regurgitation is a common finding in patients with left-sided valvular or myocardial disease, often being a marker for late-stage chronic heart failure with a grim prognosis. However, isolated tricuspid valve surgery remains infrequent and is associated with the highest mortality among all valve procedures. Hence, a largely unmet clinical need exists for less invasive therapeutic options in these patients. In recent times, multiple percutaneous therapies have been developed for treating severe tricuspid regurgitation, including tricuspid valve repair and, more recently replacement, opening an entirely new venue for managing tricuspid regurgitation. The aim of this review is to provide an updated overview and a clinical perspective on novel transcatheter tricuspid valve therapies, highlighting potential challenges and future directions. (J Am Coll Cardiol 2018;71:2935-56) © 2018 by the American College of Cardiology Foundation.

**T**ricuspid regurgitation (TR) is estimated to affect >1.5 million people in the United States (1), with a yearly incidence of about 200,000 and >300,000 patients in the United States and Europe, respectively. TR is most often functional, primarily due to annular dilatation and leaflet tethering from right ventricular remodeling caused by left-sided heart disease, atrial fibrillation, or pulmonary hypertension (2).

The prognosis of untreated TR remains poor (3), with most patients receiving lifetime medical therapy until intractable right heart failure and end-organ dysfunction appear. This is despite current guidelines favoring early tricuspid valve (TV) repair in patients with tricuspid annular dilatation undergoing left-sided cardiac surgery, even if TR is mild (4,5). Reluctance to perform tricuspid surgery

stems from increased in-hospital mortality, particularly following prior left-sided heart valve surgery (6,7) or after initial tricuspid repair (8,9). Of note, isolated TV surgery remains rare—only 5,005 isolated tricuspid procedures were performed in a large contemporary U.S. nationwide registry over a 10-year period—and continues to be associated with the highest surgical risk among all valve procedures in contemporary practice, with operative mortality rates of 8.8% to 9.7% (Figure 1) (10,11).

In recent years, a growing body of knowledge along with multiple emerging transcatheter tricuspid technologies has spurred active investigation within the interventional and surgical communities alike, with ongoing rapid momentum. We provide an updated overview of the current landscape of transcatheter TV therapies, focusing on procedural



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## ABBREVIATIONS AND ACRONYMS

<b>CAVI</b>	= caval valve implantation
<b>CE</b>	= Conformité Européenne
<b>CT</b>	= computed tomographic
<b>IVC</b>	= inferior vena cava
<b>NYHA</b>	= New York Heart Association
<b>QoL</b>	= quality of life
<b>SVC</b>	= superior vena cava
<b>TA</b>	= tricuspid annulus
<b>TR</b>	= tricuspid regurgitation
<b>TTVR</b>	= transcatheter tricuspid valve replacement
<b>TTVr</b>	= transcatheter tricuspid valve repair
<b>TV</b>	= tricuspid valve

and midterm outcomes, remaining caveats, and future directions.

## PRE-PROCEDURAL SCREENING AND MULTIMODALITY IMAGING

**TV ANATOMY.** Accurate knowledge of the TV apparatus anatomy is key when planning transcatheter tricuspid interventions. The TV is a complex structure, with several anatomic peculiarities rendering it unique (Figure 2) (12). Compared with the mitral valve, the tricuspid annulus (TA) is larger—the largest of all valves, with regurgitant orifice areas often twice those in the mitral position—and its leaflets are thinner and more fragile. The TA is a saddle-shaped ellipsoid that becomes planar and circular as it dilates. Interestingly, dilatation of the TA occurs primarily in

the anterolateral free wall in patients with left-sided heart disease with sinus rhythm, expanding mostly along the posterior border with less prominent leaflet tethering in patients with functional TR secondary to chronic atrial fibrillation (Figure 3) (13). Because of preferential dilation of the anterior and posterior leaflets, malcoaptation occurs primarily between the anteroposterior and posteroseptal commissures rather than the anteroseptal commissure, with important mechanistic and therapeutic implications for TV repair, especially for leaflet-based approaches (14).

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, or the presence of pre-existing cardiac implantable electronic devices (15).

## ECHOCARDIOGRAPHIC EVALUATION OF TR

Echocardiography remains the cornerstone imaging modality for initial assessment of the etiology and severity of TR. Current guidelines establish an

echocardiographic tricuspid annular threshold of  $\geq 40$  mm (21 mm/m<sup>2</sup>) for combined TV repair (4,5,16), although a larger cutoff (70 mm) based on direct surgical measurements has also been proposed (17). However, surgical measurements are often performed under unloaded conditions and are highly dependent on the traction applied to the TA, and recent data cast doubt on their accuracy (18). Judging the severity of TR by echocardiography remains challenging and controversial. The American Society of Echocardiography and the European Association of Cardiovascular Imaging currently consider 3 stages of functional TR: mild, moderate, and severe (Table 1) (19,20). A comprehensive description of qualitative, semiquantitative, and quantitative echocardiographic assessment of functional TR can be found elsewhere (21).

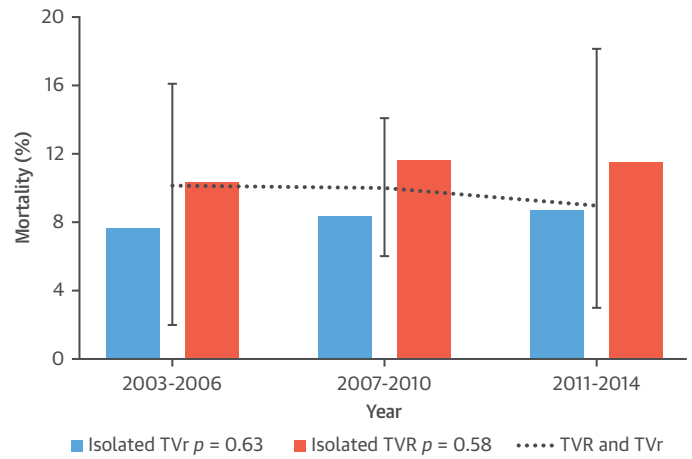
**PATIENT SELECTION.** The silent yet progressive nature of functional TR consistently leads to delayed referral of patients with end-stage heart failure with extreme leaflet tethering and tricuspid annular enlargement, carrying high perioperative mortality and adverse outcomes following correction (22). Accurate patient screening by a multidisciplinary heart team is paramount to optimize procedural results and effectiveness of transcatheter tricuspid therapies. Invasive measurement of pulmonary artery pressures and resistances can be useful when clinical and noninvasive data are inconsistent, because laminar TR and dynamic right atrial pressure in the presence of a prominent V wave may preclude reliable noninvasive estimates (23). Clinical and echocardiographic predictors of TR recurrence (TV tethering distance  $>0.76$  cm or tethering area  $>1.63$  cm<sup>2</sup> [24], higher pre-operative regurgitation grade, left and right ventricular dysfunction, permanent pacemaker, suture annuloplasty [8], increasing pulmonary pressure [25]) or worse survival (right ventricular end-systolic area  $\geq 20$  cm<sup>2</sup> [6], age, end-stage renal disease, and TV replacement [10]) after TV surgery are important factors to consider when assessing potential candidates for transcatheter TV interventions. First and foremost, efforts should focus on identifying those patients in whom transcatheter TV repair (TTVr) or transcatheter TV replacement (TTVR) is likely to be futile, heeding the dictum of *primum non nocere*. At this early stage of the technology, TTVr and TTVR should probably be reserved for patients with isolated TR deemed at too high surgical risk because of prior open heart surgery or multiple comorbidities, in the absence of severe right or left ventricular dysfunction and severe pulmonary hypertension.

### COMPUTED TOMOGRAPHIC PRE-PROCEDURAL DATA FOR PERCUTANEOUS TV INTERVENTIONS

Computed tomographic (CT) imaging has become the third-step imaging modality during pre-procedural planning for transcatheter TV interventions after transthoracic and transesophageal echocardiography (26,27), because it provides valuable anatomic spatial information of the TV apparatus sometimes hampered by echocardiography because of its complex geometry and anterior position in the chest. Of note, individually tailored contrast media protocols have been suggested to optimize CT TV imaging (28). Several specifications should be considered during CT TV assessment:

1. Tricuspid apparatus morphology: Accurate measurement of the TA, including maximal anteroposterior and septolateral diameters, perimeter, area, and right ventricular geometry, is imperative when evaluating devices that directly interact with the TV leaflets or during the screening process for TTVR. In the former, maximal distance from the TA to the right ventricular apex should also be considered (Figure 4A) (29).
2. Landing zone geometry: CT imaging is essential to identify the target anchoring site with some specific devices. In patients undergoing TV repair with some coaptation devices, the planned anchoring site is selected by drawing a perpendicular line linking the annular plane with the right ventricular septal free wall, on a sagittal reconstruction. CT imaging is also used to identify a safe landing zone and confirm adequate annular tissue and shelf for annuloplasty devices (Figure 4B) (26,30).
3. Anatomic relationships and possible impediments: CT imaging is of utmost importance when assessing surrounding structures such as the right coronary artery, especially for repair technologies targeting the TA and for TTVR (Figure 4C) (12,31). An unfavorable course of the right coronary artery ( $\leq 2$  mm from the TA) has been reported in 40% of patients with TR  $\geq 3+$  (12.5% and 27.5% at the level of the anterior and posterior tricuspid leaflets, respectively) (31). CT imaging is also an important screening tool to assess anatomic structures (large papillary muscles, trabeculations, or prominent moderator band) that would preclude successful device navigation.
4. Vascular access assessment: Sizing of the IVC in the right atrium-IVC junction plane and at the level of the first hepatic vein is paramount when

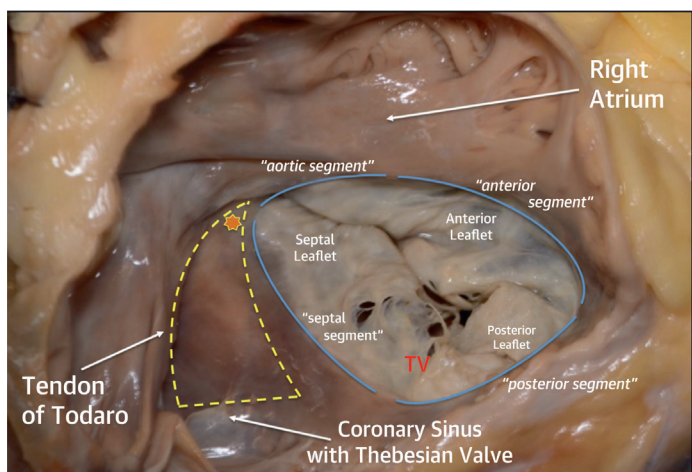
**FIGURE 1** Trends in U.S. In-Hospital Mortality After Isolated Tricuspid Valve Surgery, 2003 to 2014



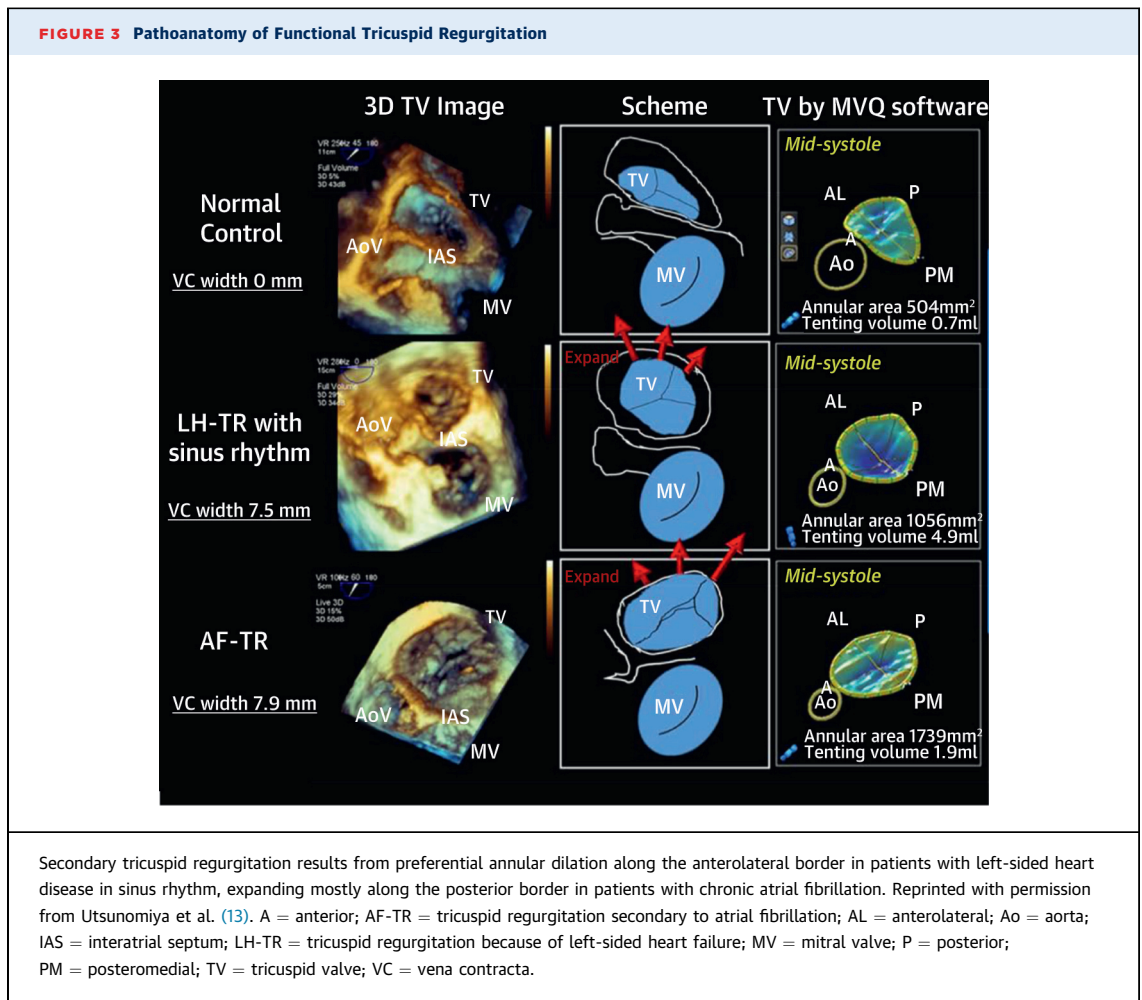
Reprinted with permission from Alqahtani et al. (11). TVR = tricuspid valve replacement; TVr = tricuspid valve repair.

planning heterotopic caval valve implantation (CAVI) procedures (Figure 4D) (32). Furthermore, the height between the junction plane and the first hepatic/accessory vein is measured to ensure for optimal valve positioning without hepatic vein obstruction. Likewise, CT imaging is also

**FIGURE 2** Tricuspid Valve and Surrounding Structures



Reprinted with permission from Taramasso et al. (12). Yellow dashed line = triangle of Koch (formed by the septal leaflet, tendon of Todaro, and coronary sinus ostium); star = atrioventricular node. TV = tricuspid valve.



essential to assess the status (size and permeability) of the venous access (jugular, subclavian, axillary veins).

5. Risk for right ventricular outflow tract obstruction: In contrast to left-sided valves, the tricuspid and pulmonary valves are open-angulated and widely separated by the crista supraventricularis, making the risk for right ventricular outflow tract obstruction almost negligible (12).
6. Predicting the best fluoroscopic projection: Similar to transaortic and transmitral valve replacement, CT imaging is helpful to provide coplanar fluoroscopic projections yielding coaxial device deployment. Two essential fluoroscopic projections have been proposed: the right anterior oblique view (obtaining a long-axis view to assess the device's trajectory and coaxiality with the TA) and the left anterior oblique caudal view (mimicking the surgical "en face" view seen from the right ventricular side) (33).

**Table 2** summarizes the most important device-specific anatomic considerations during CT pre-operative assessment.

### CARDIAC MAGNETIC RESONANCE FOR THE ASSESSMENT OF TV DISEASE

Given its excellent spatial resolution, cardiac magnetic resonance imaging represents the gold standard for quantifying right ventricular volumes and function using breath-held cine images or free-breathing, noncontrast, ECG-gated steady-state free precession sequences. Cardiac magnetic resonance might be also additive to 3-dimensional echocardiography for anatomic and functional assessment of the TV and TA. Quantifying TR severity by cardiac magnetic resonance might be performed using the indirect method by calculating TR volume (right ventricular stroke volume – forward pulmonic flow volume) or TR fraction ((TR volume/right ventricular stroke

volume] × 100) or by direct measurement of the effective regurgitant orifice area, when possible (26).

**TRANSCATHETER TV REPAIR**

Multiple technologies for TTVr are currently under preclinical or initial clinical evaluation (34). According to the anatomic therapeutic target, they can be grouped into coaptation or annuloplasty devices. Although most of these devices are still in their relative infancy, early safety and feasibility trials conducted to date have shown promising results.

**COAPTATION DEVICES. Forma.** The Forma Repair System (Edwards Lifesciences, Irvine, California) is a transcatheter option designed to increase the native leaflet coaptation surface by occupying the regurgitant orifice area. The device, a passively expandable, foam-filled balloon spacer, is advanced via the left subclavian or axillary vein through a 20- to 24-F sheath introducer and placed within the TA over a rail that is anchored at the septal portion of the right ventricular apex. The device is currently available in 3 different sizes—12, 15, and 18 mm—and is fully retrievable during all steps of the procedure (Figure 5A).

Since the initial human experience in 2015 (35), 18 patients treated under a compassionate clinical use program have been reported, with 15 patients having completed 1-year clinical follow-up (29). Successful device implantation was achieved in 16 patients (89%), with no in-hospital mortality. Among the 14 patients with successful device implantation and 1-year follow-up, improvement in New York Heart Association (NYHA) functional class was observed in 86% of patients, with significant increases in 6-min walking distance and in quality of life (QoL). Device-related thrombosis occurred in 1 patient with a subtherapeutic international normalized ratio, and there was 1 rehospitalization for heart failure. Reduction in TR from severe in 94% to moderate to severe or less in 46% was observed by 1 year.

The 30-day outcomes of the US Early Feasibility Study (n = 29) were recently reported (36). Right ventricular perforation occurred in 2 patients, and 9 patients (31%) presented at least 1 adverse 30-day event, which included death (n = 2), vascular injury (n = 1), major or life-threatening bleeding (n = 6), device-related surgery (n=3: one conversion to open-heart surgery due to perforation; two additional surgeries within the first 30 days due to device migration and infection, respectively), and acute kidney injury (n = 3). As with the compassionate-use experience, significant improvements in NYHA functional class, 6-min walking distance, and QoL were

**TABLE 1 Echocardiographic Grading of the Severity of Tricuspid Regurgitation**

	Mild	Moderate	Severe
<b>Structural</b>			
TV morphology	Normal or mildly abnormal leaflets	Moderately abnormal leaflets	Severe valve lesions
RV and RA size	Usually normal	Normal or mild dilatation	Usually dilated*
IVC diameter	Normal <2 cm	Normal or mildly dilated 2.1-2.5 cm	Dilated >2.5 cm
<b>Qualitative</b>			
Color flow jet area†	Small, narrow, central	Moderate central	Large central jet or eccentric wall-impinging jet
Flow convergence zone	Not visible, transient or small	Intermediate	Large throughout systole
CWD jet	Faint/partial/parabolic	Dense, parabolic or triangular	Dense, often triangular
<b>Semiquantitative</b>			
Color flow jet area (cm <sup>2</sup> )†	Not defined	Not defined	>10
VCW (cm)†	<0.30	0.30-0.69	≥0.70
PISA radius (cm)‡	≤0.50	0.60-0.90	>0.90
Hepatic vein flow§	Systolic dominance	Systolic blunting	Systolic flow reversal
Tricuspid inflow§	A-wave dominant	Variable	E-wave >1.0 m/s
<b>Quantitative</b>			
EROA (mm <sup>2</sup> )	<20	20-39	≥40
RVol (2D PISA) (ml)	<30	30-44	≥45

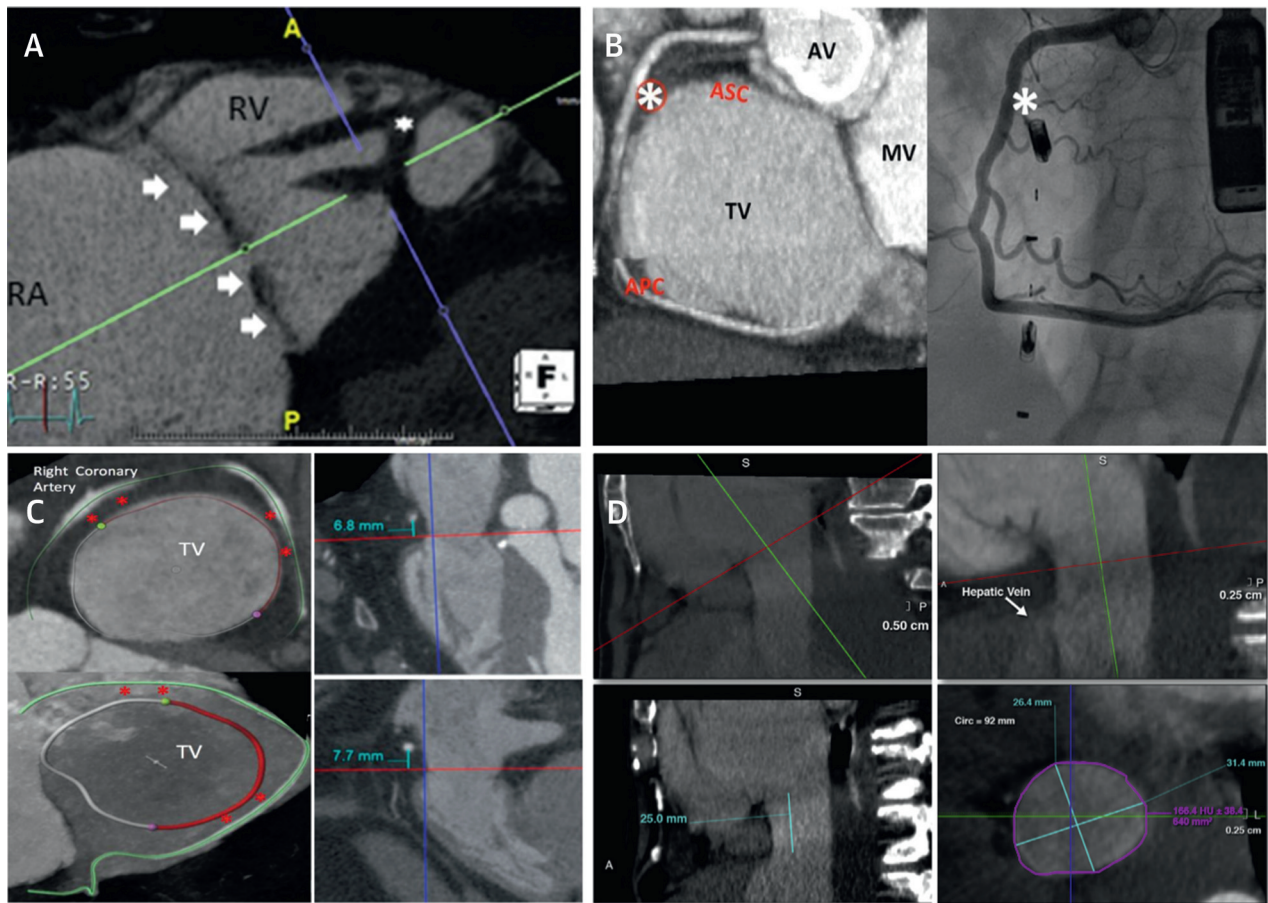
\*RV and RA size can be within the normal range in patients with acute severe TR. †With Nyquist limit >50 to 70 cm/s. ‡With baseline Nyquist limit shift of 28 cm/s. §Signs are nonspecific and are influenced by many other factors (RV diastolic function, atrial fibrillation, RA pressure). ||There are few data to support further separation of these values. Reproduced with permission from Zoghbi et al. (19).  
 CWD = continuous-wave Doppler; EROA = effective regurgitant orifice area; IVC = inferior vena cava; PISA = proximal isovelocity surface area; RA = right atrial; RV = right ventricular; RVol = regurgitant volume; TR = tricuspid regurgitation; VCW = vena contracta width.

observed at 30 days. The main clinical data from these initial experiences are summarized in Table 3.

The Forma device has been successfully used in patients with pacemakers or cardiac implantable electronic devices in situ (17% and 24% of patients included in the compassionate use and U.S. feasibility studies, respectively). However, post-procedural imaging assessment of TR severity, often complex because of the presence of multiple small noncircular jets in Forma recipients, is particularly challenging in this population. To overcome some procedural issues, next-generation Forma devices are being developed to ensure predictable anchoring while minimizing the risk for dislodgement or perforation. The ongoing European Union and Canadian SPACER (Repair of Tricuspid Valve Regurgitation Using the Edwards Tricuspid Transcatheter Repair System; NCT02787408) trial, planning to enroll 78 patients, with the primary outcome being 30-day cardiac mortality, will evaluate safety and efficacy of the Forma device and substantially extend our understanding of the Forma device performance (Table 4).



**FIGURE 4** Computed Tomographic Pre-Procedural Workup for Transcatheter Tricuspid Valve Procedures



(A) Forma: anatomic structures of the right heart: right atrium (RA), right ventricle (RV), tricuspid annular plane (white arrows), and moderator band (star). Reprinted with permission from Perlman et al. (29). (B) TriCinch: ideal target site (asterisk) between the anteroposterior commissure and midanterior on computed tomography and fluoroscopy. Reprinted with permission from Latib et al. (30). (C) Distance between the right coronary artery and the tricuspid annulus. Reprinted with permission from Taramasso et al. (12) and from van Rosendaal et al. (31). (D) Caval valve implantation: sizing is performed in the right atrium-inferior vena cava plane and at the level of the first hepatic vein. Reprinted with permission from O'Neill et al. (32). APC = anteroposterior commissure; ASC = antero-septal commissure; AV = aortic valve; MV = mitral valve; RA = right atrium; RV = right ventricle; TV = tricuspid valve.

**TriClip.** The off-label use of the MitraClip System (Abbott Vascular, Santa Clara, California) has become the first-choice approach for high-risk patients with functional TR, likely because of wide availability and operator familiarity. More than 650 procedures have already been performed worldwide, and patients receiving this therapy represent >50% of patients included in the first international registry assessing different available transcatheter TR devices (37). However, the interventional edge-to-edge repair technique faces several technical issues when applied to the tricuspid position. First, intraprocedural transesophageal echocardiography imaging of the TV might be highly challenging and somewhat limited by

its anterior location, making the use of intracardiac echocardiography an appealing alternative to ensure coaxial alignment (38). Second, steering of the MitraClip system in the right atrium is often restricted using standard techniques. The miskey technique, by inserting the clip delivery system 90° counterclockwise from its typical locking position, has been proposed to accommodate the system to the TV with an orthogonal orientation (39). Third, huge coaptation gaps are commonly found in patients with functional TR, often requiring multiple grasping attempts and clips. Grasping of the septal and anterior leaflets yielded the most favorable post-procedural outcomes in an ex vivo model (40). Indeed, tricuspid

**TABLE 2 Key Anatomic Considerations During Computed Tomographic Pre-Procedural Assessment According to Anatomic Therapeutic Target**

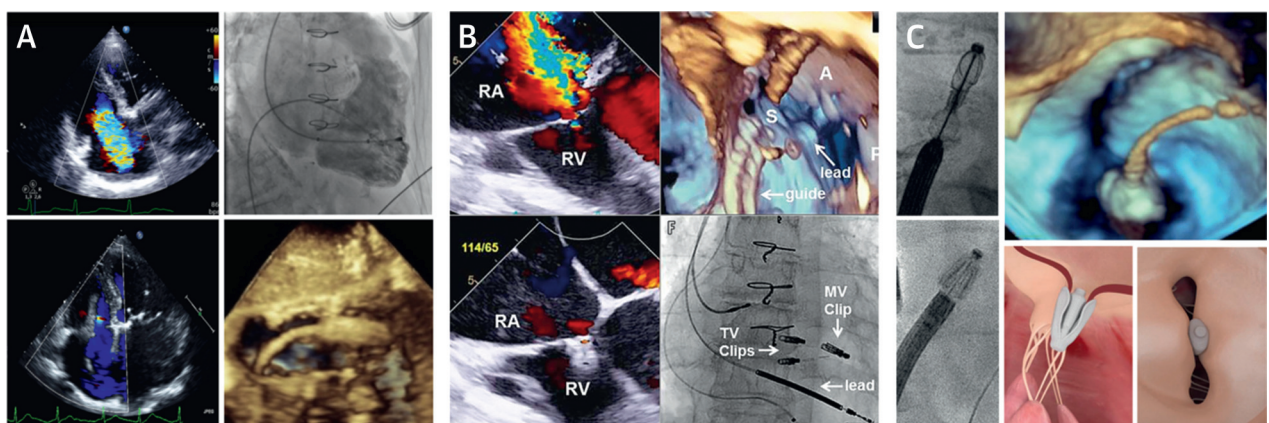
Device	Anatomic Features	Imaging Views
Coaptation devices	<ul style="list-style-type: none"> <li>Tricuspid annular dimensions (anteroposterior and septal-lateral diameters, perimeter, area), midventricular diameter</li> <li>Distance from the TA to the right ventricular apex</li> <li>Target anchoring site</li> <li>Left subclavian and axillary vein</li> </ul>	<ul style="list-style-type: none"> <li>Short axis of the TA</li> <li>Long-axis 4-chamber</li> <li>RV long-axis 2-chamber</li> <li>Coronal reconstruction</li> </ul>
Annuloplasty devices	<ul style="list-style-type: none"> <li>Course of the RCA relative to the TA</li> <li>Distance from RCA to the anterior and posterior tricuspid leaflet insertion</li> <li>Optimal anchoring target</li> </ul>	<ul style="list-style-type: none"> <li>Volume-rendered reconstruction, long-axis 2- and 4-chamber, short-axis</li> <li>Short-axis of the TA and long-axis 4-chamber</li> <li>Short-axis of the TA</li> </ul>
Heterotopic CAVI	<ul style="list-style-type: none"> <li>IVC size at the cavoatrial junction and at the level of the first hepatic vein</li> <li>Distance between the cavoatrial junction and the first hepatic vein</li> </ul>	<ul style="list-style-type: none"> <li>Double oblique transverse plane of the inferior cavoatrial junction and at the level of the first hepatic vein</li> <li>Single oblique sagittal plane of the IVC</li> </ul>
Orthotopic TTVR	<ul style="list-style-type: none"> <li>Tricuspid annular dimensions (anteroposterior and septal-lateral diameters, perimeter, area)</li> <li>Right internal jugular vein and SVC size</li> <li>Course of the RCA relative to the TA</li> <li>Distance from RCA to the anterior and posterior tricuspid leaflet insertion</li> <li>Risk for RVOT obstruction</li> </ul>	<ul style="list-style-type: none"> <li>Short axis of the TA</li> <li>Double oblique transverse plane</li> <li>Volume-rendered reconstruction, long-axis 2- and 4-chamber, short-axis</li> <li>Short-axis of the TA and long-axis 4-chamber</li> <li>Sagittal oblique reconstruction and short axis of the RVOT</li> </ul>

Adapted with permission from van Rosendaal et al. (31).  
 CAVI = caval valve implantation; RCA = right coronary artery; RVOT = right ventricular outflow tract; SVC = superior vena cava; TA = tricuspid annulus; TTVR = transcatheter tricuspid valve replacement; other abbreviations as in Table 1.

bicuspidization by using a modified “zipping technique” of the anterosseptal commissure might enable treatment of patients with extreme right ventricular dilatation or very large coaptation defects (39). Upon approximation of the leaflets with a first clip in the anterosseptal commissure (where the gap is minimum), subsequent clips are placed inward. The next-generation MitraClip XT system with longer grip arms might further facilitate the tricuspid edge-to-edge

repair. Fourth, clipping of the TV might be challenging in the presence of the pacemaker leads (Figure 5B) (41). These patients can be treated by using the aforementioned bicuspidization technique or preferably with a “triple-orifice technique,” by placing the clips between the septal and anterior as well as the septal and posterior leaflets, while avoiding grasping between the posterior and anterior leaflets (42). Last, given the reduced subvalvular

**FIGURE 5 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. (41). (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. (45). Abbreviations as in Figure 4.

**TABLE 3 Transcatheter Tricuspid Therapies: Clinical, Procedural, and Follow-Up Features**

	Forma		TriClip		Trialign		TriCinch	Cardioband	CAVI	NaviGate
	Perlman et al. (29) (n = 18)	Kodali et al. (36) (n = 29)	Nickenig et al. (43) (n = 64)	Orban et al. (44) (n = 50)	Yzeiraj et al. (49) (n = 14)	Hahn et al. (50,51) (n = 15)	Denti et al. (52) (n = 24)	Nickenig et al. (58) (n = 30)	Lauten et al. (65) (n = 25)	(n=11)*
<b>Baseline characteristics</b>										
Age, yrs	76 ± 10	76 ± 8	77 ± 10	77 ± 8	73 ± 11	74 ± 7	74 ± 8	76 ± 6	74 ± 8	76 ± 17
Female	13 (72)	19 (66)	35 (55)	20 (40)	8 (57)	13 (87)	20 (83)	22 (73)	13 (52)	5 (45)
EuroSCORE II	9.0 ± 5.7	8.1 ± 5.3	27.8 ± 16.7†	8.8 ± 6.6	16.7 ± 13.7†	NA	5.5	4.2	18.2 ± 12.9	NA
NYHA functional class ≥III	17 (94)	25 (86)	60 (94)	50 (100)	14 (100)	10 (67)	14 (58)	26 (87)	25 (100)	NA
Prior cardiac surgery	13 (72)	NA	26 (40)	NA	NA	NA	12 (50)	11 (36)	19 (76)	8 (72)
Pacemaker lead	3 (17)	7 (24)	19 (30)	14 (28)	0	0	NA	4 (13)	9 (36)	1 (9)
<b>Procedural and 30-day data</b>										
Implantation success	16 (89)	27 (93)	62 (97)	46 (92)	NA	15 (100)‡	18 (81)	30 (100)	23 (92)	10 (91)
Device embolization	1 (6)	1 (3)	0	1 (2)	NA	3 (20)	5 (23)	NA	2 (8)	0
Device-related surgery	1 (6)	3 (10)	0	1 (2)	NA	0	NA	0	2 (8)	1 (9)
TR severity ≥3	16/16 (100)	NA	49 (77)	12/46 (26)	NA	NA	11 (45)	NA	25 (100)	0
30-day mortality	0	2 (7)	3 (5)	2 (4)	0	0	0	2 (7)	3 (12)	2 (18)
<b>Follow-up data</b>										
Follow-up time, mo	12	1	1	6	NA	12	6	1	10	3
TR severity ≥3	12/13 (92)	NA	49 (77)	9/39 (23)	NA	NA	(~75)	NA	(100)	0
NYHA functional classes I and II	11/14 (79)	18/25 (72)	24 (37)	25/39 (64)	NA	9/10 (90)	NA	23/28 (82)	NA	NA
Δ6MWT, m	84	39	16	84	NA	49	130	31	NA	NA
Mortality	0	2 (7)	3 (5)	8 (16)	NA	1 (7)	0	2 (7)	14/22 (63)	3 (27)

Values are mean ± SD or n/N (%). \*Courtesy from Dr J.L. Navia (Cleveland Clinic, Cleveland, Ohio), unpublished data. †Logistic EuroSCORE (%). ‡1 patient requiring right coronary artery stenting.  
6MWT = 6-min walking test; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NA = not available; NYHA = New York Heart Association; other abbreviations as in Tables 1 and 2.

space in the right ventricle, slow movements of the clip delivery system are needed to avoid entanglement with the TV leaflets and chords.

In a multicenter European registry reported by Nickenig et al. (43), 64 high-risk patients with moderate to severe TR (88% functional) underwent TV clipping (of these, 22 patients underwent concomitant mitral repair). Procedural success was 97% (≥2 clips in ~50% of cases, ~80% at the antero-septal commissure), with ≥1 TR grade reduction in 91% of patients. No serious intraprocedural complications occurred, with 3 in-hospital deaths (5%). Most patients showed significant post-procedural improvements in TR severity and NYHA functional class, as well as exercise capacity enhancement at 30-day follow-up. Orban et al. (44) recently reported the 6-month outcomes of 50 patients treated with the transcatheter edge-to-edge TV repair technique, 36 of whom underwent concomitant mitral valve repair. Procedural success was achieved in 46 patients (92%), with a mean of 1.9 clips per patient, 84% being positioned between the anterior and septal leaflets. At 6-month follow-up, improvement of ≥1 NYHA functional class and ≥1 TR grade was observed in 79% and 90% of patients, respectively, with TR grade ≤2+ in 77% of the patients and a 16% mortality rate. The chief clinical and procedural features of patients treated with the MitraClip system are outlined in Table 3.

The ongoing TRILUMINATE Conformité Européenne (CE) Mark Trial (Trial to Evaluate Treatment With Abbott Transcatheter Clip Repair System in Patients with Moderate or Greater Tricuspid Regurgitation; NCT03227757) will prospectively enroll 75 subjects in up to 25 European Union and U.S. sites with up to 3-year follow-up to further evaluate performance of this approach (Table 4).

**Pascal.** The Edwards Pascal transcatheter mitral valve repair system (Edwards Lifesciences) integrates technical aspects from the Forma and the MitraClip devices by combining a 10-mm central spacer and 2 paddles (~25 mm width) and clasps (10 mm length) that attach the device to the valve leaflets, thus overcoming possible limitations of the former devices separately. The system is composed of a 22-F steerable guide sheath, a steerable catheter, and an implantation catheter. The device is repositionable and recapturable if needed (Figure 5C). The first-in-human experience of the Edwards Pascal system in patients with severe mitral regurgitation showed the feasibility and promising preliminary efficacy data (45). The first successful case of TTVr using the Pascal for treating severe TR was recently reported (46). This leaflet coaptation device provides a new appealing option for TTVr to be evaluated in further studies.



**TABLE 4 Summary of Ongoing and Future Studies on Transcatheter Therapies for Tricuspid Regurgitation**

Device	Study	Study Design	Patients	Primary Endpoints
Forma	SPACER (NCT02787408)	Prospective registry	78	Safety: cardiac mortality at 30 days, compared with a research-derived performance goal based on high-risk surgical outcomes for tricuspid repair/replacement
	Early Feasibility Study of the Edwards Forma Tricuspid Transcatheter Repair System (NCT02471807)	Prospective registry	30	Procedural success defined as device success and freedom from device- or procedure-related SAEs at 30 days
MitraClip	TRILUMINATE (NCT03227757)	Prospective registry	75	Echocardiographic tricuspid regurgitation reduction at least 1 grade (30 days) Composite of MAE (6 months)
	MitraClip for Severe TR (NCT02863549)	Prospective registry	100	Tricuspid regurgitation grade and incidence of major adverse cerebrovascular events (1-12 months)
Trialign	SCOUT II (NCT03225612)	Prospective registry	60	All-cause mortality at 30 days
	Early feasibility of the Mitralign PTVAS, also known as Trialign (NCT02574650)	Prospective registry	30	Technical success at 30 days, defined as freedom from death with successful access, delivery and retrieval of the device delivery system, and deployment and correct positioning of the intended device, and no need for additional unplanned or emergency surgery or reintervention related to the device or access procedure
TriCinch	PREVENT (NCT02098200)	Prospective registry	24	Safety: participants with MAE* within 30 days of the procedure Efficacy: reduction of tricuspid regurgitation by at least 1 degree immediately after the procedure and at discharge
	Clinical Trial Evaluation of the Percutaneous 4Tech TriCinch Coil Tricuspid Valve Repair System (NCT03294200)	Prospective registry	90	All-cause mortality of the per protocol cohort at 30 days post-procedure
MIA	STTAR (not registered)	Prospective registry	40	Safety: rate of MAEs at 30-day follow-up Performance: technical success rate of MIA implant and reduction in the valve area
Cardioband	TRI-REPAIR (NCT02981953)	Prospective registry	30	Overall rate of major SAEs and serious adverse device effects at 30 days Intraprocedural successful access, deployment and positioning of the Cardioband device and septolateral diameter reduction Change in septolateral dimension at 30 days
	Edwards Cardioband Tricuspid Valve Reconstruction System Early Feasibility Study (NCT03382457)	Prospective registry	15	Freedom from device or procedure-related adverse events (30 days)
Heterotopic CAVI	HOVER (NCT02339974)	Prospective registry	15	Procedural success at 30 days, defined as device success and no SAE† Individual success at 30 days, defined by device success and positive clinical outcomes‡
	TRICAVAL (NCT02387697)	Randomized open-label	40	Maximum relative Vo <sub>2</sub> at 3 mo (difference of means in maximum relative Vo <sub>2</sub> at 3 months compared with control group)

\*Including death, Q-wave myocardial infarction, cardiac tamponade, cardiac surgery for failed TriCinch implantation, stroke, and septicemia. †Including all death, all stroke, myocardial infarction, acute kidney injury grade 3, life-threatening bleeding, major vascular complications, pericardial effusion or tamponade requiring drainage, and vena cava syndrome. ‡Positive clinical outcomes defined as no readmissions to hospital for right-sided heart failure or right-sided heart failure equivalents including drainage of ascites or pleural effusions, new listing for heart transplantation, VAD, or other mechanical support; improvement in 1 of 3 variables: KCCQ improvement >15 versus baseline and 6MWT improvement >70 m versus baseline, or Vo<sub>2</sub> peak improvement >6% versus baseline.

HOVER = Heterotopic Implantation of the Edwards-SAPIEN Transcatheter Aortic Valve in the Inferior Vena Cava for the Treatment of Severe Tricuspid Regurgitation; KCCQ = Kansas City Cardiomyopathy Questionnaire; MAE = major adverse event; MIA = minimally invasive annuloplasty; PREVENT = Percutaneous Treatment of Tricuspid Valve Regurgitation With the TriCinch System; PTVAS = percutaneous tricuspid valve annuloplasty system; SAE = serious adverse event; SCOUT = Safety and Performance of the Trialign Percutaneous Tricuspid Valve Annuloplasty System; SPACER = Repair of Tricuspid Valve Regurgitation Using the Edwards Tricuspid Transcatheter Repair System; STTAR = Study of Transcatheter Tricuspid Annular Repair; TRICAVAL = Treatment of Severe Secondary Tricuspid Regurgitation in Patients With Advanced Heart Failure With Caval Vein Implantation of the Edwards SAPIEN XT Valve; TRILUMINATE = Evaluation of Treatment With Abbott Transcatheter Clip Repair System in Patients With Moderate or Greater Tricuspid Regurgitation; TRI-REPAIR = Tricuspid Regurgitation Repair With Cardioband Transcatheter System; VAD = ventricular assist device; Vo<sub>2</sub> = oxygen consumption; other abbreviations as in Tables 2 and 3.

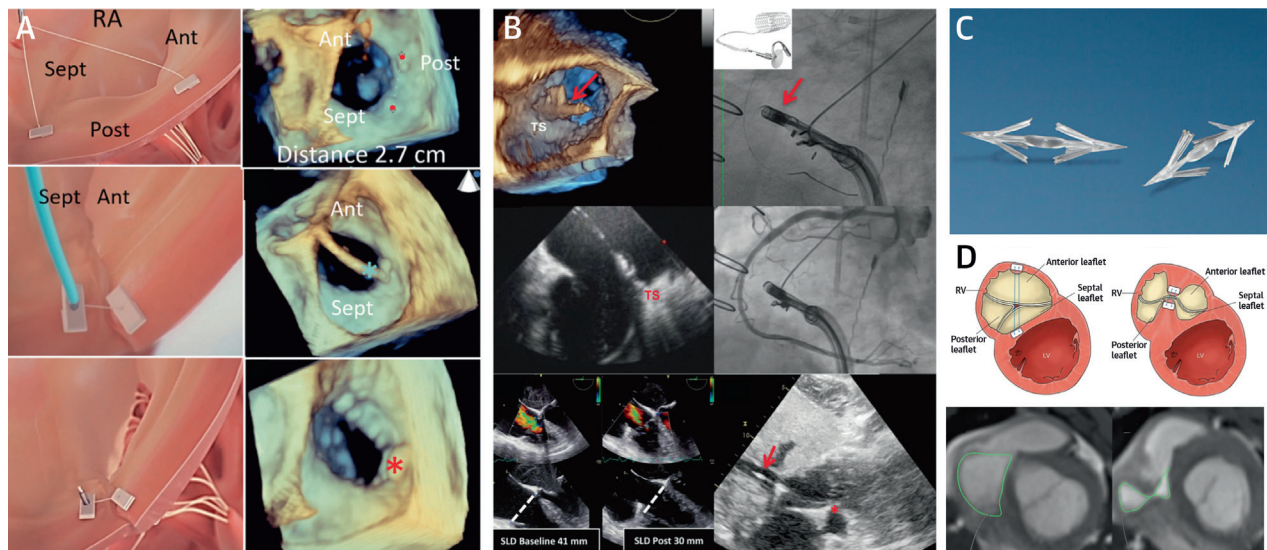
**ANNULOPLASTY DEVICES.** Most percutaneous annuloplasty devices reproduce well-established surgical techniques addressing the chief pathophysiological mechanism of secondary TR. Transcatheter annular-based systems can be categorized as direct suture (Trialign, TriCinch, minimally invasive annuloplasty, pledget-assisted suture tricuspid annuloplasty) or ring (direct: Cardioband, Millipede IRIS; indirect: transatrial intrapericardial tricuspid annuloplasty) annuloplasty devices (47). Whereas better long-term outcomes should theoretically be expected with the latter, suture annuloplasty devices have gained a wider clinical experience to date.

**Suture annuloplasty systems. Trialign.** The Trialign device (Mitralign, Tewksbury, Massachusetts) is a

transcatheter annuloplasty system that mimics the modified Kay bicuspidization surgical procedure, thus obliterating the posterior tricuspid leaflet. A deflectable catheter is first introduced through a transjugular approach to advance an insulated radiofrequency wire across the TA. Two pledgets are sequentially fixed at the posteroseptal and anteroposterior commissures and thereafter cinched together using a dedicated plication lock device, thus resulting in posterior leaflet plication and TV bicuspidization. A second pair of pledgets might be implanted to obtain a greater annular reduction (Figure 6A) (48).

The first multicenter experience, including 14 patients with moderate to severe TR (86% functional) treated with the Trialign device for compassionate

**FIGURE 6** 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 pliated 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. (50). **(B)** TriCinch. Transesophageal echocardiographic and fluoroscopic visualization of the device (**red arrow**) in the right atrium; right coronary angiography. Significant reduction of septolateral annular diameter (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. (27). **(C)** Picture of MIA (minimally invasive annuloplasty technology), reprinted with permission from Micro Interventional Devices; investigational device only. **(D)** Plectet-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. (55).

use, showed marked post-procedural alleviation of TR (reductions of 42%, 51%, and 34% in vena contracta, effective regurgitant orifice area, and annular area, respectively), with a single procedural complication (arrhythmia) (49). The SCOUT I (Early Feasibility of the Mitralign Percutaneous Tricuspid Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation) feasibility trial, enrolled 15 symptomatic patients with at least moderate functional TR undergoing tricuspid annuloplasty with the Trialign device in the United States. Implantation success was achieved in all patients, with 93% procedural success (1 patient requiring right coronary artery stenting because of extrinsic compression) and 80% technical success at 30 days (3 instances of single-pledget dehiscence without reintervention). At 30-day follow-up, no major adverse events had occurred, with significant reduction in tricuspid annular area and effective regurgitant orifice area and significant improvements in functional class (intention-to-treat cohort: reduction of  $\geq 1$  degree in NYHA functional class,  $p = 0.001$ ; 6-min walking distance:  $245.2 \pm 110.1$  m to  $298.0 \pm 107.6$  m,  $p = 0.008$ ) and Minnesota Living With Heart

Failure Questionnaire (intention-to-treat cohort:  $47.4 \pm 17.6$  to  $20.9 \pm 14.8$ ,  $p < 0.001$ ) (50). At 12-month follow-up, 1 patient died (not device related) and another required elective reintervention, with sustained improvements in NYHA status (90% in class I or II) and QoL (intention-to-treat: from 47.4 to 25.5,  $p = 0.013$ ; as-treated group: from  $49.6 \pm 15.7$  to  $19.2 \pm 12.4$ ,  $p = 0.003$ ) (51). **Table 3** outlines the main features of these studies.

The ongoing SCOUT II CE mark study will include up to 60 patients from 15 U.S. and European sites, with up to 5-year follow-up (**Table 4**).

**TriCinch.** The TriCinch system (4Tech Cardio, Galway, Ireland) is a Kay-like annuloplasty system that reduces the septolateral diameter of the TA by cinching at the anteroposterior commissure. An 18-F steerable delivery system is first advanced through a 24-F femoral vein introducer sheath into the right atrium. A corkscrew anchor is then fixed near the anteroposterior commissure. After right coronary angiography, a self-expanding stent, connected to the anchor through a Dacron band, is deployed in the subhepatic region of the IVC, ensuring maintenance of the tension applied to the TV (**Figure 6B**).

Preliminary data from the first 24 patients treated with the first-generation TriCinch Screw Tip device in the PREVENT (Percutaneous Treatment of Tricuspid Valve Regurgitation With the TriCinch System) trial were reported. The device was successfully implanted in 18 patients (81%), with significant ( $\geq 1$  grade) acute TR reduction in 94% of cases. Hemopericardium occurred in 2 patients (8%), while 5 patients (23%) experienced late annular anchor detachment. Preliminary data showed severe 4+ TR reduction from  $\sim 80\%$  to  $\sim 40\%$ , with sustained improvement in functional class and QoL at 6-month follow-up (Table 3) (52).

Because of stability concerns, the second-generation TriCinch Coil System using an alternative coil anchoring system (replacing the previous corkscrew) has been developed. A hemispiral-shaped anchor is delivered in the pericardial space, thus providing increased surface area, tensioning, and stability. Following successful preclinical testing in 65 acute and chronic animals, the first-in-human case with the second-generation TriCinch device has been performed with no procedural complications and 30-day improvement in TR severity and QoL (53).

**Minimally invasive annuloplasty.** Minimally invasive annuloplasty technology (MIA, Micro Interventional Devices, Newtown, Pennsylvania) is a sutureless transcatheter annuloplasty system composed of a thermoplastic elastomer (MyoLast) and low-mass polymeric, compliant, self-tensioning anchors (PolyCor), allowing TV annular reduction (Figure 6C). The device is surgically implanted through a 16-F steerable delivery system that allows deployment of the device in a  $270^\circ$  partial ring pattern. The STTAR (Study of Transcatheter Tricuspid Annular Repair) trial will enroll 40 patients to assess the safety and efficacy of the minimally invasive annuloplasty device (Table 4). To date, 5 patients have been included in the surgical arm of the study, 2 of them using a bicuspidization approach. All patients were successfully treated, with no procedural adverse events and significant reduction of TV area. Early launching of the percutaneous arm of the STTAR study is expected (54).

**Pledget-assisted suture tricuspid annuloplasty.** Transcatheter pledget-assisted suture tricuspid annuloplasty is a transannular “double-bite” pledgeted suture technique that reproduces the Hetzer double-orifice suture technique. Using marketed devices, 2 sutures and 1 pledget are sequentially placed at the midanterior and the posteroseptal TA. Each suture is tightened using a Cor-Knot device (31 cm, LSI Solutions, New York, New York) (Figure 6D) (55).

The first human compassionate-use cases were recently reported (56).

**Ring annuloplasty systems. Cardioband.** The Cardioband Tricuspid Repair System (Edwards Lifesciences) is a direct, sutureless, and adjustable surgical-like Dacron band, based on the CE-approved device for mitral regurgitation treatment. The device is inserted through a transfemoral 24-F access sheath, and up to 17 anchors are deployed on the atrial side of the anterior and posterior TA to fix the device. A size adjustment tool enabling bidirectional reshaping of the TA is advanced over a wire, and the band is then cinched, providing a controlled reduction of the anteroposterior and septolateral TA diameters (Figure 7A) (57).

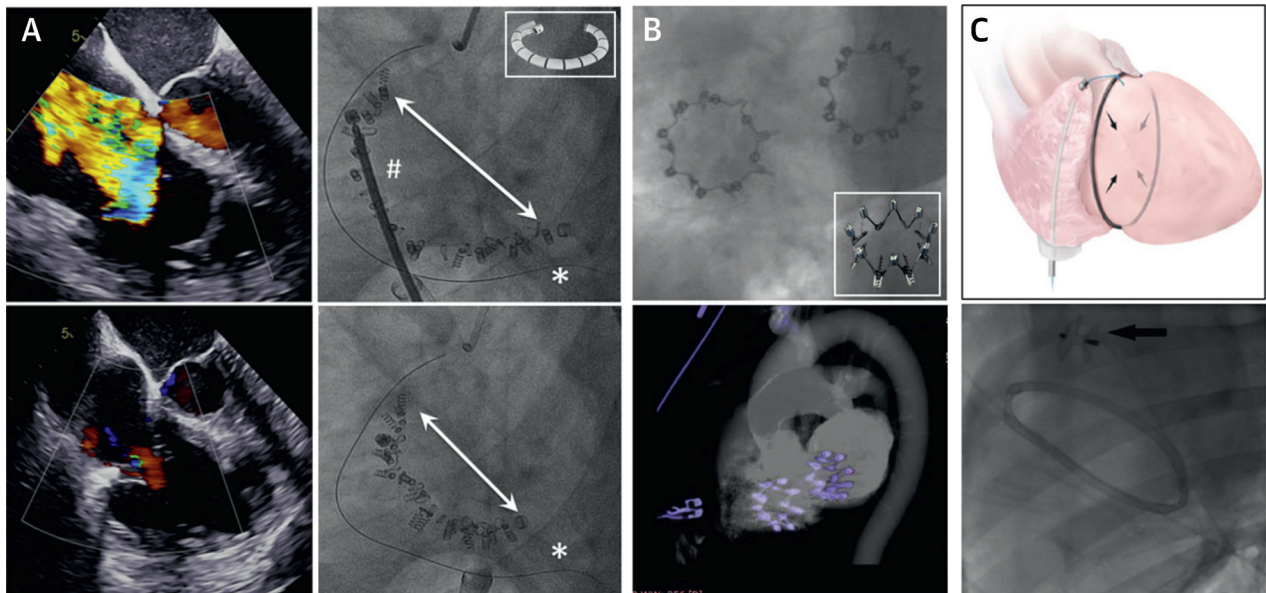
The 30-day outcomes of the first-in-human TRI-REPAIR (Tricuspid Regurgitation Repair with Cardioband Transcatheter System; NCT02981953) CE EU trial were recently reported (Table 3) (58). Among 30 patients with functional TR  $\geq 2+$  and annular diameter  $\geq 40$  mm, procedural success was achieved in all patients, with a 17% average reduction in septolateral diameter. Periprocedural events included 2 deaths (right ventricular failure, life-threatening bleeding unrelated to device), 1 stroke, and 3 major bleedings. At 30 days, significant reductions in effective regurgitant orifice area (50%) and vena contracta (31%) were observed, with improvements in stroke volume (7%) and functional status. Enrollment of a further 30 patients is ongoing.

**Millipede IRIS.** The Millipede IRIS system (Boston Scientific, Marlborough, Massachusetts) is a complete, adjustable, semirigid annuloplasty ring that mimics the surgical gold-standard complete annuloplasty ring for treatment of both functional mitral and TR. The device consists of a zigzag-frame collapsible nitinol ring, with individual collars at each zigzag’s peak and corkscrew-shaped anchors attaching the ring to the fibrous annulus. The device is fully repositionable and retrievable. The anchor near the atrioventricular node is removed to minimize the risk for conduction disturbances.

The IRIS ring has been surgically implanted in the TV in 2 patients undergoing concomitant mitral valve repair, showing a sustained TA diameter reduction of about 40%, with no TR after 12 months (Figure 7B, Table 3) (59). A dedicated transcatheter delivery system for the TV IRIS ring is currently being developed. The device requires no anticoagulation and preserves the native anatomy, enabling other concomitant or future percutaneous options as well as serving as a dock for implantation of a transcatheter heart valve.

**Transatrial intrapericardial tricuspid annuloplasty.** Transatrial intrapericardial tricuspid annuloplasty is an indirect, fully retrievable, transpericardial

**FIGURE 7** Ring Annuloplasty Systems



**(A)** Cardioband system. Transesophageal echocardiographic and fluoroscopic images before and after cinching of the Cardioband. #Cardioband cinching catheter. \*Coronary wire in the right coronary artery. Reprinted with permission from Schueler et al. (57). **(B)** Millipede. Fluoroscopic and computed tomographic imaging of a double implant of the Millipede device in the tricuspid and mitral position. Courtesy of Dr. Jason Rogers, University of California, Davis, Medical Center (Sacramento, California). **(C)** The transatrial intrapericardial tricuspid annuloplasty system. Illustration and fluoroscopy showing the device implanted in the atrioventricular groove, final right atrial appendage closure with a nitinol closure device (arrow). Reprinted with permission from Rogers et al. (60).

annuloplasty system under preclinical evaluation. A memory-shaped delivery system is advanced through the femoral vein into the pericardium through a right atrial appendage puncture. An adjustable circumferential implant is then placed along the atrioventricular groove, exerting external compression over the TA from the pericardial space. The right atrial appendage puncture is finally sealed using a nitinol occluder (Figure 7C). The device was successfully implanted in preclinical experience in 16 swine with functional TR, leading to significant TV geometry changes (reductions in annular area and perimeter, increase in coaptation length) (60). A newer version of the device—including a balloon anchor pericardial sheath, the annuloplasty system, and a bioresorbable closure device—for human use is currently being developed by the National Institutes of Health and Cook Medical (Bloomington, Indiana). An early feasibility study is planned for 2018 (61).

#### HETEROTOPIC CAVI

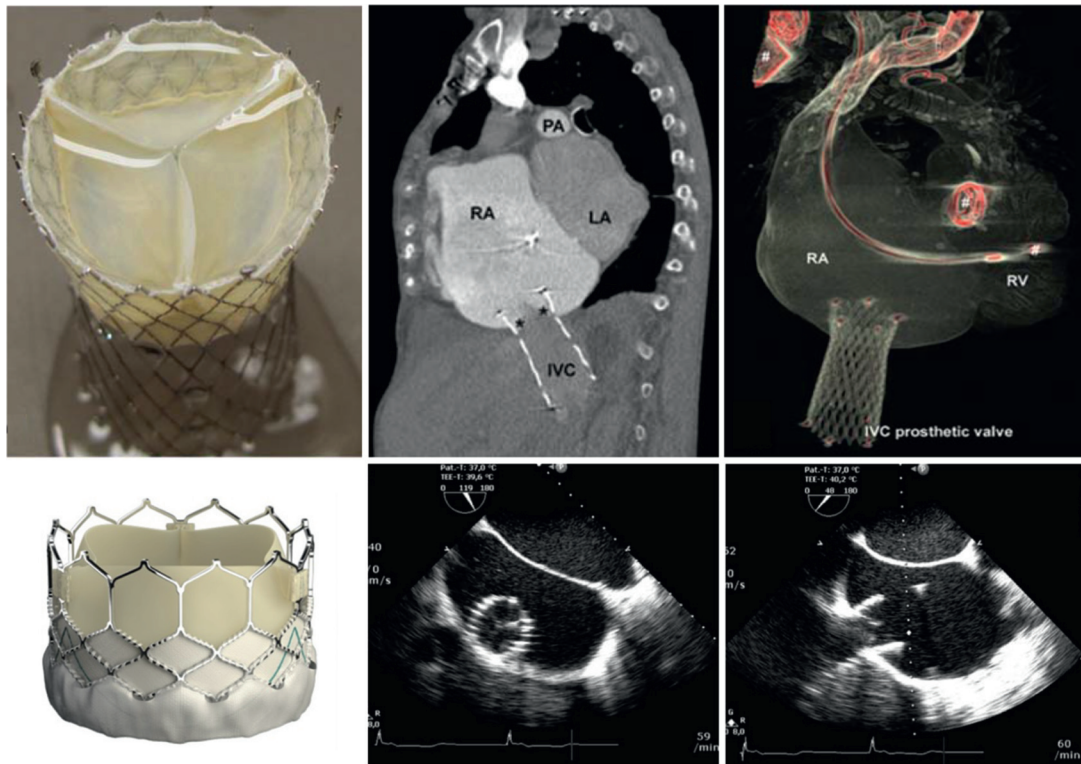
The objective of heterotopic CAVI, which does not specifically address the severity of TR *per se*, is to

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 29-mm balloon-expandable SAPIEN valve (Edwards Lifesciences) was first reported by Laule et al. (62). 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 ( $\leq 29$  mm), balloon-expandable CAVI should preferably be restricted to IVC only (for IVC diameters  $\leq 30$  mm). Furthermore, considering the low-pressure system, lifelong anticoagulation is often required.



**FIGURE 8** Heterotopic Caval Valve Implantation



The self-expandable TricValve and the Edwards SAPIEN balloon-expandable valve. Computed tomographic angiography, 3-dimensional reconstruction, echocardiographic short- and long-axis views after device implantation. Reprinted with permission from Lauten et al. (63). IVC = inferior vena cava; LA = left atrium; PA = pulmonary artery; RA = right atrium; RV = right ventricle.

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) (63,64). Implantation of the TricValve can be safely performed using a single- or dual-valve approach, with landing zone diameters  $\leq 35$  mm. The maximum available sizes are 38 and 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 (Table 3) (65). 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

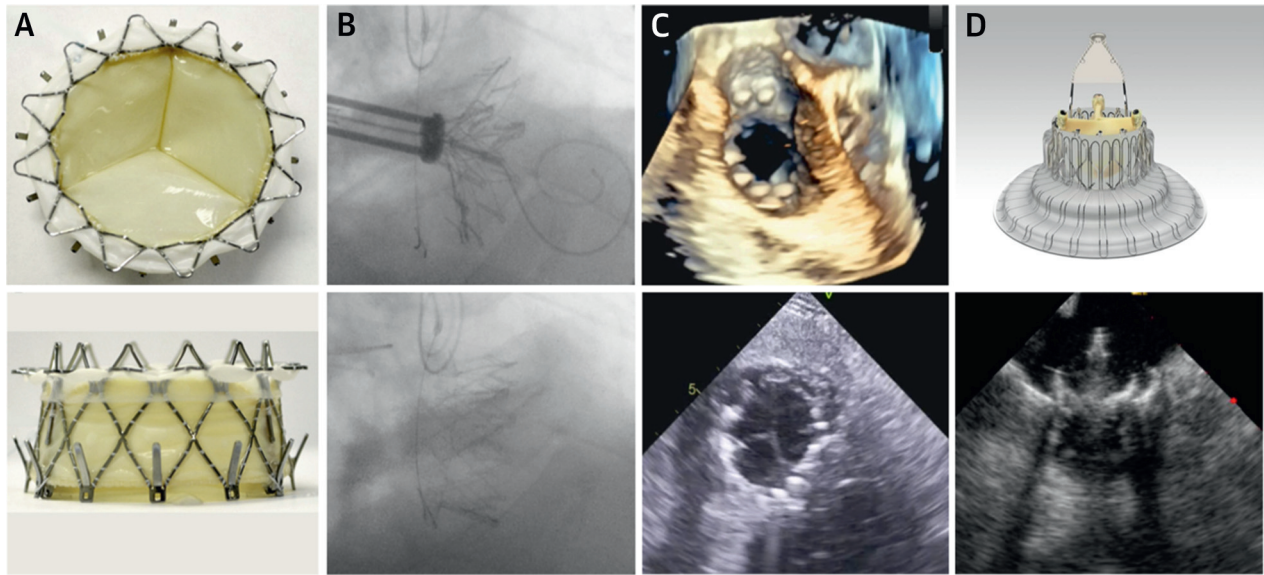
pressure in the IVC and right atrium) were observed, with no detrimental impact on cardiac index. Thirty-day mortality was 12% (3 of 25), with high 1-year mortality (14 of 22 [63%]) due mainly to high comorbid burden.

Despite being the first transcatheter TV therapy used in humans (63), 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 [65,66]) 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).

#### TTVR

Since the first preclinical experience with a dedicated self-expandable bioprosthetic TV in 8 ewes reported in 2005 by Boudjemline et al. (67), preclinical models

**FIGURE 9** Orthotopic Transcatheter Tricuspid Valve Replacement



**(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).

with fully percutaneous TTVR platforms have been scarce (68).

The first case of TTVR in a human native TV was reported in 2014 by Kefer et al. (69) 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 9A to 9C). 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  $\geq 15$  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 70° 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 (70). 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. (71) in November 2016 and April 2017, in a

**TABLE 5 Initial Global Clinical Experience With Transcatheter Tricuspid Therapies (n = 282)**

<b>Patient characteristics</b>	
Age, yrs	76 ± 9
Female, %	60 (40-87)
EuroSCORE II	8.8 ± 7.5
Functional TR, %	96 (86-100)
NYHA functional class ≥III, %	90 (58-100)
Prior cardiac surgery, %	51 (36-76)
Pacemaker lead, %	22 (0-36)
Atrial fibrillation, %	85 (67-93)
<b>Devices</b>	
MitraClip	114 (40)
Forma	47 (17)
Cardioband	30 (11)
Trialign	29 (10)
CAVI	25 (9)
TriCinch	24 (9)
NaviGate	11 (4)
Millipede	2 (1)
<b>Procedural data</b>	
Successful implantation, %	93 (81-100)
Device embolization, %	6 (0-23)
Conversion to open heart surgery, %	2 (0-9)
<b>30-day outcomes</b>	
TR severity ≥3, %	60 (0-100)
NYHA functional class I and II, %	62 (37-90)
ΔGMWT, m	47 (16-130)
Mortality, %	5 (0-18)

Values are weighted mean ± SD, weighted mean (range), or n (%), derived from previously presented data in [Table 3](#) (29,36,43,44,49,50,52,58,59,65,72). Abbreviations as in [Tables 1 to 3](#).

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 Therapeutics meeting (72). 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 ([Table 3](#)). 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 post-operative 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 transtricuspid 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](#)) (73). 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. The overall main patient characteristics and procedural and 30-day outcomes reported with currently available transcatheter TV therapies to date are summarized in [Table 5](#). 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 trans-tricuspid leads, which did not preclude procedural success among those devices specifically targeting leaflet coaptation (29,39,43). Interestingly, recent

experiences have shown the feasibility of TTVr in patients with pacemaker leads using annuloplasty systems, such as the Cardioband and Trialign devices (58,74).

Transcatheter treatment of TR was associated with high procedural success rates (>90%) and relatively low procedure-related complications (2% conversion to open heart surgery, 6% device dislodgement). This is particularly reassuring if we consider that most of these first-generation devices are still in their relative infancy, and many of them were (initially) transcatheter mitral devices that were used in the tricuspid space. To date, the average 30-day mortality rate following transcatheter tricuspid therapies has been 5.1%. These outcomes compare favorably with the recently reported 8.8% and 9.7% in-hospital mortality rates in 2 contemporary series evaluating outcomes of isolated TV surgery from 2003 to 2014 among 5,005 and 1,364 patients, respectively (10,11).

A common finding among most early studies conducted to date with transcatheter therapies addressing functional TR correction in severely enlarged native TVs has been the presence of marked improvements in functional status (~60% of patients in NYHA functional class I or II, average increase of ~50 m in 6-min walking distance) and QoL, despite modest reductions in TR (at least moderate residual TR in 60% of patients). In contrast to transcatheter aortic valve replacement, residual mild to moderate regurgitation may be judged acceptable for compassionate patients with advanced heart failure status often presenting with long-standing torrential TR, with scant therapeutic options. However, the results regarding residual TR are still clearly inferior to those obtained with surgery, and this may translate into negative hemodynamic and clinical effects at mid- to long-term follow-up. Future studies are needed to determine the minimal degree of TR improvement associated with improved symptoms and clinical outcomes.

Thus far, on the basis of data from the very early experiences reported to date (Table 5) and in agreement with those reported by Taramasso et al. (37) in the international TriValve Registry, transcatheter TV therapies should be reserved for high-risk patients, with symptomatic functional TR, before extreme dilatation of the right ventricle and leaflet tethering occur. Of keen interest, remarkable plasticity of the right ventricle and TA has been shown in response to TR regression, leading to important geometric changes (reduction in TA diameter and TV tenting,

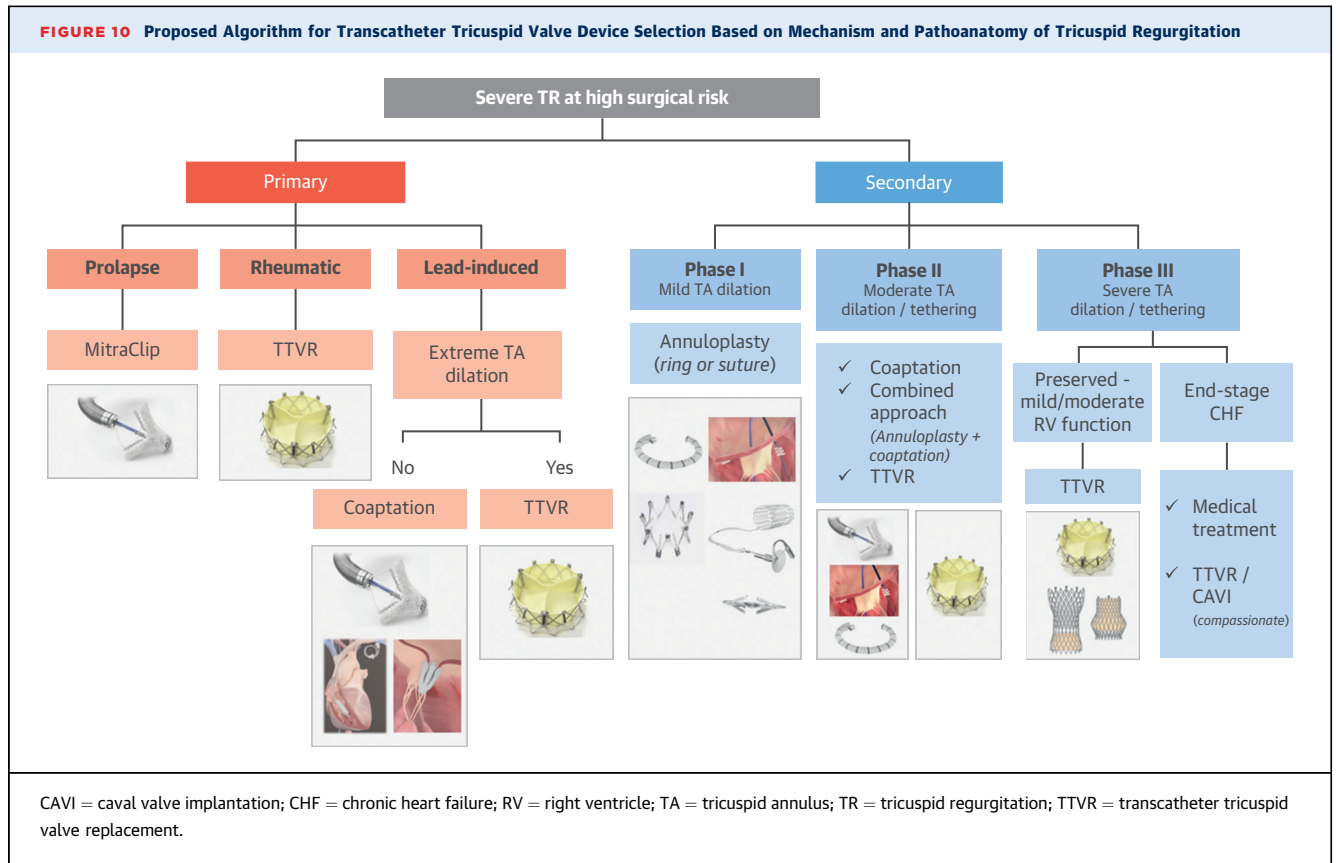
reverse right ventricular remodeling, and increased TV coverage) (75). Considering that a more aggressive approach for TR treatment is increasingly promoted, a shift toward a less symptomatic target population with moderate to severe TR with tricuspid annular dilatation ought to be expected in coming years. Determining the subset of patients who may benefit from earlier intervention, as well as the potential role for dynamic training of the right ventricle linked to progressive TR reduction with emerging transcatheter therapies, will require further evaluation.

**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 bioprote-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 dilatation, as well as for rheumatic TR.

Secondary TR has been divided into 3 stages for therapeutic purposes (76). In the early stage, initial dilatation of the right ventricle leads to tricuspid annular dilatation 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 (77,78). In the second stage, progressive right ventricular and tricuspid annular dilatation 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 (79,80). Interestingly, the use of the NaviGate bio-prosthesis 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 (81). 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. A potential strategy to choose transcatheter TV treatment on the basis of mechanisms and patient-specific anatomy is proposed (Figure 10).

**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 (82), 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.

**Standardized definitions and endpoints in forthcoming studies.** The lack of consistency in definitions, efficacy, and safety endpoints used in studies assessing transcatheter TR therapies precludes an accurate comparison between different available devices and approaches. Of note, the implementation of traditional endpoints used in previous trials on aortic or mitral valvular disease may not be appropriate in this unique and extremely sick target population. Future trial designs evaluating transcatheter therapies in this advanced heart failure population should probably focus on reduction in TR grade, diuretic down-titration, improvements in specific QoL measurements, and enhanced functional capacity as an endpoint, in addition to harder endpoints such as death or heart failure hospitalization. Also, it is imperative to standardize definitions and specific outcomes in this patient population, highlighting the need for a specific tricuspid academic research consortium that would enable accurate and uniform interpretation and comparison between clinical studies, as have been adopted for transcatheter aortic and mitral valve interventions (83,84).

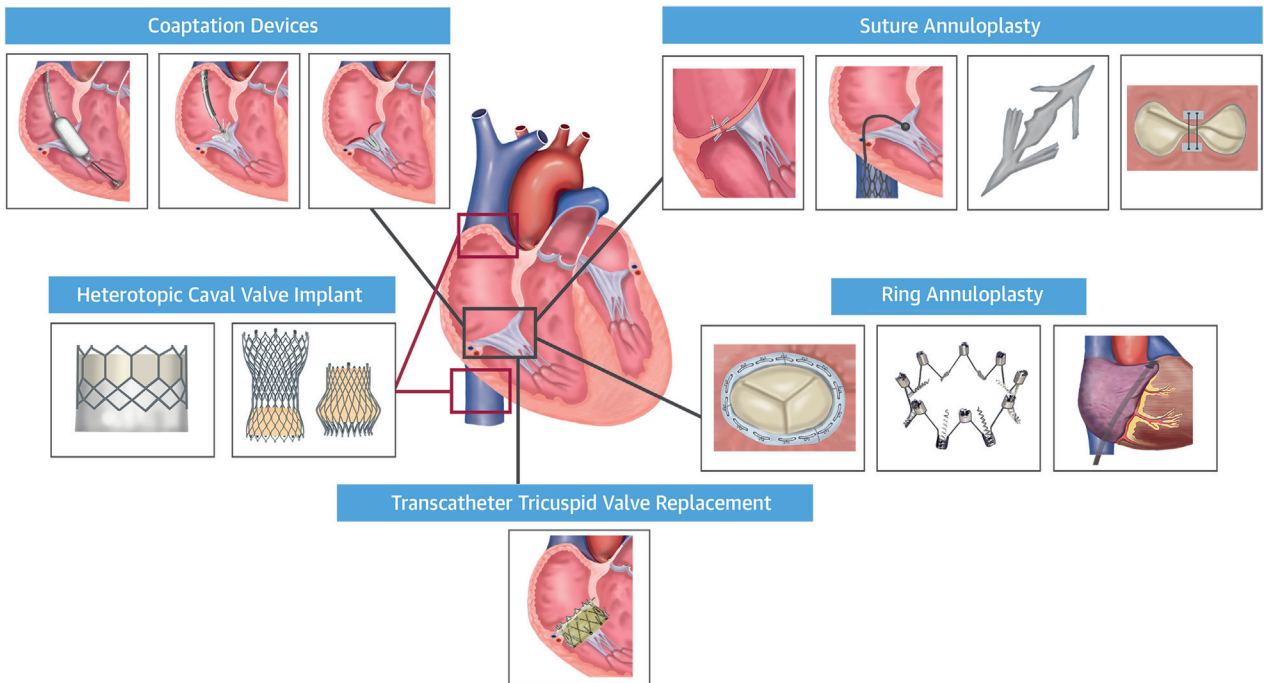
**Tricuspid-specific risk scores.** Determining patient eligibility for transcatheter TV procedures is one of the major decision issues to be faced. Several risk scores have been validated to determine short-term morbidity and mortality after cardiac surgery. The European System for Cardiac Operative Risk Evaluation II score and the Society of Thoracic Surgeons score are the most widely used scores in contemporary practice (85,86). Although initially designed and validated to predict mortality in cardiac surgical cohorts, their use has been accepted for transcatheter aortic and mitral valve interventions. Likewise, most initial studies assessing transcatheter devices for treating TR have used the same risk scoring systems. Nonetheless, adoption of the Society of Thoracic Surgeons score in the tricuspid space might be improper, as it has not been previously validated for TV surgery. Recently, novel specific scores for isolated TV surgery have been proposed, although not validated yet (87). Identification and validation of novel dedicated risk scoring systems should translate

into a more refined and tailored risk stratification and improved patient selection.

**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 (78), as well as for TV replacement over repair (88). 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 (10). 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 (5). 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.

### CENTRAL ILLUSTRATION Transcatheter Tricuspid Landscape



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Coaptation devices (Forma, MitraClip, Pascal), suture annuloplasty (Trialign, TriCinch, minimally invasive annuloplasty technology, pledget-assisted suture annuloplasty), ring annuloplasty (Cardioband, Millipede, transatrial intrapericardial tricuspid annuloplasty), heterotopic caval valve implantation (SAPIEN, TricValve), and transcatheter tricuspid valve replacement (NaviGate).

### CONCLUSIONS

Despite the increase in the number of TV procedures observed in the past decade, isolated TV surgery remains infrequent and continues to be associated with one of the highest risks among all cardiac valve procedures in contemporary practice. This has resulted in a large number of untreated TR patients. In response to this unmet clinical need, several less invasive transcatheter-based therapies addressing different anatomic therapeutic targets have emerged as an alternative to surgery in high-risk patients with functional TR (**Central Illustration**). Although the field is still in its infancy, multiple studies have already shown the feasibility and safety of different transcatheter TV therapies. Preliminary efficacy data has also shown significant improvements in functional status and QoL, despite modest reductions in TR according to conventional definitions following TTVr. The recent first-in-human cases of orthotopic TTVr, with no or

minimal residual TR in most cases, represent a landmark step forward in the transcatheter treatment of TR. Steady device innovation and iteration together with increased experience are anticipated to improve procedural and clinical outcomes in the coming years. Nevertheless, selection of optimal intervention timing, standardized TR grading schemes and definitions, and long-term clinical outcomes and device performance durability remain important caveats that need to be addressed in future trials.

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