Tricuspid Valve Academic Research Consortium Definitions for Tricuspid Regurgitation and Trial Endpoints

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Abstract

Interest in the pathophysiology, etiology, management, and outcomes of patients with tricuspid regurgitation (TR) has grown in the wake of multiple natural history studies showing progressively worse outcomes associated with increasing TR severity, even after adjusting for multiple comorbidities. Historically, isolated tricuspid valve surgery has been associated with high in-hospital mortality rates, leading to the development of transcatheter treatment options. The aim of this first Tricuspid Valve Academic Research Consortium document is to standardize definitions of disease etiology and severity, as well as endpoints for trials that aim to address the gaps in our knowledge related to identification and management of patients with TR. Standardizing endpoints for trials should provide consistency and enable meaningful comparisons between clinical trials. A second Tricuspid Valve Academic Research Consortium document will focus on further defining trial endpoints and will discuss trial design options.

Keywords   transcatheter • treatment • tricuspid regurgitation

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Highlights

- There is an independent relationship between increasing TR and worse outcomes, but gaps exist in understanding of pathophysiology, diagnosis, and treatment.
- Refinement of classification categories, novel methods for assessing and grading TR, and better selection of outcome measures should inform the design of clinical trials.
- This document provides recommendations for classification of disease etiology, standardized definitions and methods to assess disease severity, and trial endpoints.
- Transcatheter alternatives to surgical intervention are under investigation; yet, more work is needed to define patient selection criteria, goals of therapy, and clinical outcomes.

Abbreviations and Acronyms

3D-VCA	3-dimensional vena contracta area
A-STR	atrial secondary tricuspid regurgitation
CIED	cardiac implantable electronic device
CMR	cardiac magnetic resonance
CT	computed tomography
EROA	effective regurgitant orifice area
LTR-A	lead-associated tricuspid regurgitation, type A
LTR-B	lead-associated tricuspid regurgitation, type B
PA	pulmonary artery
PH	pulmonary hypertension
PISA	proximal isovelocity surface area
RA	right atrium/atrial
RV	right ventricle/ventricular
RVEF	right ventricular ejection fraction
sPAP	systolic pulmonary artery pressure
TAPSE	tricuspid annular plane systolic excursion
TR	tricuspid regurgitation
T-TEER	tricuspid transcatheter edge-to-edge repair
TTVI	transcatheter tricuspid valve intervention
V-STR	ventricular secondary tricuspid regurgitation

Interest in the pathophysiology, etiology, management, and outcomes of patients with tricuspid regurgitation (TR) has grown significantly over the last 10 years given the natural history studies showing a high disease prevalence[1–3] and poor outcomes associated with increasing TR severity, even after adjusting for comorbidities.[3–5] However, a number of gaps in our understanding of the disease as well as the rapid expansion of transcatheter solutions for structural heart disease have increased the need for further research and trials. Indications for isolated tricuspid valve (TV) surgery have poor penetration into clinical practice, which may be related to reported high in-hospital mortality rates, partly associated with late clinical diagnosis.[6] Transcatheter alternatives to surgical intervention are being investigated; yet, appropriate patient selection, goals of therapy, and clinically meaningful outcomes are unknown.

Considering these challenges, standardized clinical trial pathways and endpoint definitions to evaluate treatment outcomes in TR patients are needed. The Heart Valve Collaboratory is a multidisciplinary community of physicians, regulators, industry partners, an d patient advocates who organized a comprehensive meeting to define the knowledge gaps in our understanding of TR, standardize definitions and methods to assess disease severity, and develop feasible and efficient trial designs. This first Tricuspid Valve Academic Research Consortium (TVARC) document describes the current understanding of the disease state, natural history, and treatment options. The paper includes a proposal for general categories of clinical trial endpoints. A second planned TVARC document will focus on further defining trial endpoints and discusses trial design options.

Importantly, TVARC is not a guideline intended to influence clinical practice, but is a document intended to inform clinical research and, in particular, clinical trials. Unlike a guideline, which must rely on evidence-based medicine for recommendations, this document aims to standardize trial endpoints to address gaps in our knowledge related to identification and management of patients with TR. Standardizing endpoints for trials should provide consistency across trials and may strengthen the evidence required for guideline recommendations. Given the dynamic field of TR therapeutics, our understanding of its disease state will likely increase with time, and as treatment options expand, trial design and endpoints will undoubtedly evolve. This document is, therefore, intended to be a "living document," which will allow periodic updating as our knowledge expands.

Standardizing terminology in valve intervention

In the current literature, various abbreviations are used for the description of transcatheter valve procedures. *Table 1* shows standardized common abbreviations within this academic research consortium.

Table 1 **Suggested Standardized Abbreviations in the Context of Tricuspid Valve Interventions**

Abbreviation	Full Name	Description
TTVI	Transcatheter tricuspid valve intervention	To be used for any tricuspid valve repair or replacement technique
TTVR	Transcatheter tricuspid valve replacement	To be used for any tricuspid valve replacement, including orthotopic and heterotopic techniques
T-TEER	Tricuspid valve transcatheter edge-to-edge repair	To be used for tricuspid leaflet-based edge-to-edge repair techniques
TTV Repair	Transcatheter tricuspid valve repair	To be used for any tricuspid valve repair technique
A-STR	Atrial secondary tricuspid regurgitant	To be used to indicate secondary tricuspid regurgitation with atrial/annular dilatation as the main mechanism of regurgitation
V-STR	Ventricular secondary tricuspid regurgitation	To be used to indicate secondary tricuspid regurgitation with ventricular dilatation/dysfunction as the main mechanism of regurgitation
PTR	Primary tricuspid regurgitation	To be used to indicate tricuspid regurgitation caused by leaflet abnormalities
LTR-A	Lead-associated tricuspid regurgitation, type A	To be used to indicate tricuspid regurgitation caused by cardiac implantable electronic device caused regurgitation
LTR-B	Lead-associated tricuspid regurgitation, type B	To be used to indicate tricuspid regurgitation not related directly to cardiac implantable electronic device

Section 1: Disease State Considerations

TR classification and clinical presentation

TR classification

Historically, TR is viewed as a binary classification, which includes primary TR, where leaflet abnormalities are the cause of regurgitation, and secondary diseases, where leaflets are normal but structural changes of the annulus or right ventricle (RV) result in insufficient leaflet coaptation. Currently, a more comprehensive classification system for TR etiologies more appropriately encompasses the pathophysiology of this multifaceted disease (Table 2, Figure 1).[7,8] Different TR etiologies may be associated with disparate outcomes,[9–12] supporting a refinement of current classification categories. The main changes to the TR mechanistic classification scheme include the following: 1) subdividing secondary TR into atrial secondary tricuspid regurgitation (A-STR) and ventricular secondary tricuspid regurgitation (V-STR); 2) creating a separate category for TR associated with cardiac implantable electronic device (CIED) leads, labeled as lead-associated tricuspid regurgitation (LTR); and 3) subcategorizing LTR into type A (LTR-A), whose CIED lead is causing the TR, and type B (LTR-B), whose CIED lead is incidental (Table 2, Figure 1). Each mechanism of secondary TR may be identified by morphologic changes that occur as a result of the pathophysiologic changes associated with a particular disease process.

Given the recent literature suggesting that patients with A-STR have different outcomes compared with V-STR,[11,12] defining this etiologic category for trials may be important. Table 3 provides suggested anatomic and functional parameters for defining an A-STR phenotype based on current literature,[12,13] understanding the following: 1) normative data from a large registry suggests consideration of sex-based cutoffs[14,15]; and 2) V-STR is a heterogeneous population, and the primary disease process will determine the combination of findings that define V-STR. For instance, invasive measures of pulmonary vascular hemodynamics will differ depending on whether the patient has precapillary or postcapillary pulmonary hypertension. Likewise, patients with primary RV cardiomyopathies and V-STR may have normal LV function. The main morphologic and hemodynamic characteristics of A-STR include absence of significant leaflet tethering, marked dilatation of the right atrium (RA) in the setting of relatively normal RV size and function, as well as normal LV function and absence of pulmonary hypertension. It is likely there will be a population of patients who have some features of A-STR and some of V-STR, and thus cannot be clearly categorized. Further research may help determine if a "mixed" morphology is a separate population of patients with different outcomes.

TR severity assessment

Echocardiography is the most widely used imaging modality to assess TR severity, TV anatomy, and RV function. The American Society of Echocardiography Guidelines recommend a multiparametric and hierarchical approach to TR assessment, which culminates in a 3-class grading scheme (mild [1+], moderate [2+], and severe [3+])[16] that continues to be used clinically. The increasing mortality risk associated with increasing TR severity[17,18] supports an extended grading scheme.[19] Initial early feasibility studies[20–22,23] and a recent randomized controlled trial of transcatheter device therapy[24] show utility to the subclassification or extension of the "severe" grade of TR to severe (3+), massive (4+), and torrential (5+). The degree of symptom improvement parallels the TR grade reduction when using the 5-grade scale.[24] The European Society of Cardiology and European Association of Cardiovascular Imaging guidelines state that the further subclassification of patients referred for transcatheter interventions with "severe" disease into "severe, massive and torrential," may have prognostic significance.[8,25] TVARC supports the use of the 5-grade scheme in this context, noting that the extended grading scheme was specifically developed for patients entering into transcatheter device therapy trials to refine TR reduction endpoint criteria. Table 4 shows qualitative, semiquantitative,

Table 2 Classification of TR by Cause and Presenting Abnormalities

Causative Disease Process	Etiology	Tricuspid Valve/RV Morphology	Carpentier Classification
Primary TR (5%-10% of patients)			
Degenerative disease	Prolapse or flail leaflet	Abnormal leaflet mobility, normal RV	II
Congenital	Apical displacement of leaflet attachment (ie, Ebstein's anomaly)	Abnormal leaflet position, atrialized RV	I or IIIb
Acquired (ie, tumors, trauma, carcinoid, RHD, radiation)	Leaflet Injury (ie, tumor, trauma, biopsy, lead extraction) or infiltration/fibrosis (ie, carcinoid, rheumatic disease, radiation valvulopathy)	Abnormal leaflet morphology/mobility, normal RV	I or IIIa
Secondary TR[a] (~80% of patients)			
Ventricular secondary TR			
Left ventricular disease	Postcapillary PH (HFpEF, HFrEF)	RV dilatation (spherical remodeling)/ dysfunctional → leaflet tethering, dilated RA/TA	I or IIIb
Left heart valvular disease	Postcapillary PH		I or IIIb
Pulmonary disease	Precapillary PH (chronic lung disease, CTEPH, PAH)		I or IIIb
RV dysfunction/remodeling	RV dilatation and dysfunction (ie, RV infarct, RV dysplasia)		IIIb
Atrial secondary TR			
RA/TA dilatation[a]	RA/TA dilatation (ie, related to age, atrial fibrillation, HFpEF)	RA dilatation/dysfunction → TA dilatation (minimal leaflet tethering), conical RV remodeling	I
CIED-related TR (~10%-15%)			
LTR-A (causative)	Leaflet impingement, perforation, valvular/subvalvular adhesions/restriction	Tricuspid leaflet tethering/adhesions	I or IIIb
LTR-B (incidental)[b]	CIED present without tricuspid valve apparatus interference	Morphology dependent on primary disease process	I, II, or III

CIED = cardiovascular implantable electronic device; CTEPH = chronic thromboembolic pulmonary hypertension; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LTR = lead-related tricuspid regurgitation; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RA = right atrial; RHD = rheumatic heart disease; RV = right ventricular; TA = tricuspid annular; TR = tricuspid regurgitation.
[a]Chronic TR may result in RV remodeling with subsequent leaflet tethering.
[b]CIED may be present and although not the causative mechanism of tricuspid regurgitation, may impact transcatheter device choice.

and quantitative echocardiographic parameters with relevant cutoff values for the 5-grade TR severity.

Current imaging guidelines recommend quantifying TR severity whenever possible.[8] The proximal isovelocity surface area (PISA) flow convergence method is most commonly used and is associated with outcomes.[4,17,26] Several methodologic limitations of this calculation are known to result in underestimation of the effective regurgitant orifice area (EROA).[27–29] The new 5-grade TR severity scheme, which may be used for clinical trials, suggests different cutoffs reflecting the underestimation of EROA by the PISA method compared with direct measurement of 3-dimensional vena contracta area (3D-VCA). This underestimation may be reduced by correcting for the tethering angle of the valve leaflet and the relative low velocity of the tricuspid regurgitant jet.[30] In addition, studies of quantitative Doppler methods for measuring regurgitant volume and calculating EROA have shown good correlation with 3D-VCA[27,31] but require further validation. The current recommended methods of quantifying TR, as well as a proposed method by quantitative Doppler, are shown in *Figure 2*.

Although limitations of individual echocardiographic methods exist, the multiparametric and hierarchical approach proposed by imaging guidelines performs well when compared with cardiac magnetic resonance (CMR).[8,25,32] Limitations of CMR and quantitation of RV stroke volume raise questions about the accuracy of the method.[16] Risk stratification by CMR quantitative indexes of TR severity[33] require further validation. Cardiac computed tomography (CT) angiography–based chamber volumes are similar to those derived from CMR,[34] and CT may offer confirmatory evidence of TR severity.

Due to the dynamic nature of TR during respiration, echocardiographic measurements should ideally be made at end-expiration in spontaneously breathing patients, when alveolar pressure is near zero. The dependency on volume load as well as the responsiveness to diuretic therapy also should be considered when grading TR by any imaging modality. Accordingly, TR assessment should ideally be performed when patients are euvolemic, on stable diuretic therapy, with optimized pulmonary pressure and normal systemic blood pressure. The role of exercise testing remains an unexplored tool. An important
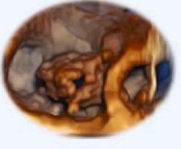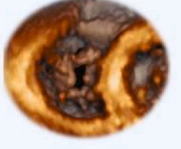
Parameter	Secondary		CIED (A)	Primary	
2D TTE					
3D TTE					
Parameter	Ventricular	Atrial	CIED Type A	Primary TR	
Carpentier Class	IIIb	I	I, IIIa, IIIb	Prolapse II	RHD IIIa
TV Tethering	++++	+/−	++	−	−
Leaflet Restriction	Systole	−	Systole/Diastole	−	Diastole
RA/TA Dilatation	++	++++	+/−	++	+++
RV Dilatation	+++	+/−	+/−	+/−	+/−
RV Dysfunction	+++	+/−	+/−	+/−	+/−

Figure 1 Classification of TR Etiology

The expanded tricuspid regurgitation (TR) classification by etiology currently separates secondary TR into atrial secondary and ventricular secondary disease. When cardiac implantable electronic device (CIED) leads are present, lead-associated TR may be subcategorized into type A, whose CIED is causing the TR, and type B, whose CIED is incidental. 2D = 2-dimensional; 3D = 3-dimensional; RA = right atrium; RV = right ventricle; TA = tricuspid annulus; TTE = transthoracic echocardiography; RHD = rheumatic heart disease; TV = tricuspid valve. Modified from Hahn RT, Badano LP, Bartko PE, et al. Tricuspid regurgitation: recent advances in understanding pathophysiology, severity grading and outcome. *Eur Heart J Cardiovasc Imaging.* 2022;21;23(7):913–929.

consequence of significant TR is the reduction of forward stroke volume, which may then affect the accurate assessment of concomitant valvular diseases.[35,36] Significant TR is more common with low-flow, low-gradient aortic stenosis and is associated with poor outcomes.[37] Low flow may also cause underestimation of the echocardiographic assessment of mitral regurgitation and mitral stenosis.[38] Following device therapy of TR, there may be an improvement of forward flow,[39] which may change the hemodynamic quantitation of concomitant valvular disease.

Because the tricuspid annulus is much larger than the mitral annulus, tricuspid stenosis (TS) is much less likely to occur after surgical or transcatheter annuloplasty or tricuspid transcatheter edge-to-edge repair (T-TEER), and gradients have not been associated with outcomes following T-TEER.[40] In contrast, TS can occur after transcatheter valve replacement, because of leaflet thrombosis, structural valve deterioration, or possibly prosthesis-patient mismatch. The minimum echocardiographic parameters that should be assessed are continuous wave Doppler measurements of peak and mean transtricuspid diastolic gradients, peak and mean transtricuspid systolic (eg, regurgitant) gradients, and the diastolic velocity time integral (VTI). Although for native TVs, an effective orifice area (EOA) by continuity equation of ≤ 1 cm^2, velocity time integral > 60 cm, mean gradient ≥ 5 mm Hg, and pressure half-time ≥ 190 ms are suggestive of TS, there are different cutoffs reported for surgical bioprostheses as well as transcatheter valve-in-surgical valve.

Multimodality imaging assessment and follow-up recommendations are listed in Supplemental Table 1.

TR clinical presentation

Clinically, right heart failure associated with TR can be characterized by the following: 1) systemic fluid retention, which may lead to elevated jugular venous pressure, peripheral edema, ascites, hepatic distention, reduced intestinal absorption, and anasarca; 2) decreased systolic reserve and low cardiac output, resulting in exercise intolerance, dyspnea, and fatigue; and 3) atrial or ventricular arrhythmias. Significant chronic TR is associated with signs and symptoms of profound reduction in cardiac output including malnutrition, anemia, and reduced cognitive function.[41] The downstream consequences of chronic severe TR and right heart failure include chronic kidney disease (cardiorenal syndrome) and liver disease (cardiohepatic syndrome) (Supplemental Table 2), and, less commonly, protein-losing enteropathy.

Outcomes of untreated TR

Although TR was considered benign for decades, multiple studies now suggest that increasing severity of TR is associated with progressively worse outcomes regardless of pulmonary artery (PA) pressure and left ventricular ejection fraction.[5] A recent large retrospective analysis suggests that even mild TR is associated with worse outcomes

Table 3 Suggested Anatomic and Functional Parameters to Define Atrial and Ventricular Secondary Tricuspid Regurgitation[a]

	A-STR Phenotype[b]	V-STR Phenotype[b]
Leaflet morphology[c]		
Tenting height (4Ch), mm	≤9	> 9
Tenting area (4Ch), cm^2	<2.1	≥2.1
Tenting volume, mL	<2.5[d]	≥2.5
Right heart chamber size[c]		
RV midventricular diameter, mm	≤38[d]	>38
RV midventricular diameter index, mm/m^2	<21	≥21
RV end-diastolic volume index, mL/m^2	<80	≥80
RV end-systolic volume index, mL/m^2	<21	≥21
2D sphericity index[e]	<55	≥55
End-systolic RA to RV area ratio[e]	≥1.5	<1.5
Right ventricular systolic function[c]		
TAPSE, mm	>17	≤17
FAC, %	≥35	<35
RVFWS, %	≥20	<20
RV TDI S', cm/s	≥9	<9
3D RVEF, %	≥50	<50
LVEF	≥50[d]	Variable[f]
Invasive pulmonary vascular hemodynamics[c]		
PCWP, mm Hg	≤15	Variable[f]
mPAP, mm Hg	<20	Usually >20[f]
PVR, WU	<2.0	Variable[f]

2D = 2-dimensional; 3D = 3-dimensional; 4Ch = 4-chamber view; A-STR = atrial secondary tricuspid regurgitation; FAC = fractional area change; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right atrium/atrial; RV = right ventricle; RVEF = right ventricular ejection fraction; RVFWS = right ventricular free wall strain; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; V-STR = ventricular secondary tricuspid regurgitation.

[a]This is a ctoonsensus recommendation of TVARC and the PCR Tricuspid Focus Group.
[b]Assumes no primary TR or CIED-causative TR.
[c]In the setting of discordant measures within the anatomic or functional categories, an integrative approach should be used to define A-STR (absence of significant leaflet tethering in the setting of a dilated right atrium, and normal RV size and function) and V-STR (significant leaflet tethering with dilated RV). Note: within each category, the volumetric assessment and the indexed values may be preferred for research studies when available.
[d]From Schlotter et al.[12]
[e]From Florescu et al.[49]
[f]Critieria cannot be strictly defined given the heterogeneous etiologies of V-STR (ie, precapillary, postcapillary or combined precapillary/postcapillary pulmonary hypertension, and primary RV cardiomyopathies).

Recent studies have attempted to isolate TR from potential confounders and to assess outcomes for individual etiologies separately. For primary etiologies, TR associated with rheumatic disease,[42] flail leaflets, and pacemaker leads[43] is associated with adverse outcomes, even when adjusted for RV dysfunction. Although A-STR is associated with excess mortality in adjusted analyses,[44,45] recent studies show that outcomes are worse for patients with V-STR.[11,12]

Current guidelines give a Class I recommendation for concomitant TV intervention at the time of left heart surgery when severe TR or annular dilatation is present.[13,25] A recent randomized trial questions this practice showing that at the time of mitral valve repair, concomitant repair of moderate TR but not mild TR with annular dilatation is associated with reduction in TR progression.[46]

Right heart response to TR

Significant TR causes right heart volume overload leading to dilatation of the RA, tricuspid annulus,[47] and RV.[48] The resulting papillary muscle displacement and change in the right heart axis further worsen TR and lead to a vicious cycle characterized by progressive RV dilation, RV dysfunction, and clinical deterioration (*Figure 3*).[44]

Assessment of RV size, shape, and function

The assessment of RV size and function is helpful in distinguishing the different morphologic etiologies of STR: A-STR is associated with conical RV remodeling compared with V-STR, which is associated with spherical remodeling and midventricular dilatation.[49] RV function and size are usually assessed by transthoracic echocardiography (*Tables 5* and *6*, respectively). Normal values of RV size from current guidelines are shown in *Table 6*; however, recently, the World Alliance of Societies of Echocardiography study has published normative values for RV size and function based on age, sex, and ethnicity, which may be important considerations in clinical trials.[14,15] One of the most useful correlates of RV function remains tricuspid annular plane systolic excursion (TAPSE), which characterizes the longitudinal shortening of the RV which typically accounts for ~80% of RV stroke volume. Three-dimensional echocardiography assessment of RV ejection fraction can predict outcomes in patients with cardiovascular disease[50] and may be superior to TAPSE in patients following transcatheter tricuspid valve intervention (TTVI).[51] Both RV and RA strain may also be prognostically important in patients with significant TR.[52] Although current imaging guidelines do not define grades of severity in RV dysfunction, a proposal for possible cutoffs to be used in clinical trials is shown in *Table 7*, and is based on guideline-reported normal mean ± SD,[53] multinational reports of normative data,[15] as well as outcomes studies,[54] and will require validation, particularly given the load dependence of these measurements.

CT provides a more precise anatomic visualization of cardiac anatomy and adjacent structures. CT imaging of the right heart, vena cava, and right coronary artery are prerequisites for the appropriate selection and sizing of several transcatheter devices. CMR remains the most reproducible method for assessing chamber volumes, ejection fraction, as well as myocardial structural changes, and may have utility in patients with TR. Multimodality imaging assessment of the right heart is summarized in *Supplemental Table 3*.

Assessment of pulmonary vascular pathophysiology

An assessment of PA pressures is essential for understanding TR pathophysiology. Precapillary pulmonary hypertension (PH) in patients with severe TR has also been associated with worse outcomes following

compared with none/trace TR.[3] However, assessments of comorbidities and RV function were limited, raising concern that TR may simply be a surrogate marker for other cardiac or systemic comorbidities.

Table 4 **Echocardiographic Parameters and Relative Cutoffs for TR 5-Tier Grading**

	Mild (1+)	Moderate (2+)	Severe (3+)	Massive (4+)	Torrential (5+)
Qualitative					
Tricuspid morphology	Normal or mildly abnormal	Moderately abnormal	Severely abnormal (flail leaflet, large coaptation gap, marked tethering)		
Color-flow jet area	Small, narrow, central	Moderate central	Large central, or eccentric, wall impinging		
Flow convergence zone	Not visible, transient, or small	Intermediate in size and duration	Large throughout systole		
CWD contour	Faint, partial, parabolic	Dense, parabolic	Dense, parabolic or triangular	Dense, often triangular, may have low peak velocity	Dense, usually triangular, often low peak velocity
Right heart dimensions	Usually normal	Normal or mild dilatation	Usually dilated	Dilated	
Semiquantitative					
VCW (biplane), mm[a]	<3	3–6.9	7–13.9	14–20.9	≥21
PISA radius, mm[b]	≤5.4	5.5–8.9	≥9		
Hepatic vein flow[c]	Systolic dominant	Systolic blunting	Systolic flow reversal		
Tricuspid inflow (PWD)	A-wave dominant	Variable	E-wave dominant (≥1 m/s)		
Quantitative					
PISA EROA, mm^2	<20	20–39	40–59	60–79	≥80
Regurgitant volume (2D PISA), mL	<30	30–44	45–59	60–74	≥75
New quantitative methods					
Regurgitant fraction, %	≤15	16–49	≥50		
3D VCA, mm^2	—	—	75–94.9	95–114.9	≥115
2D Doppler EROA, mm^2	—	—	75–94.9	95–114.9	≥115

CWD = continuous-wave Doppler; EROA = effective regurgitant orifice area; PISA = proximal isovelocity surface area; PWD = pulsed-wave Doppler; VCA = vena contracta area; VCW = vena contracta width; other abbreviations as in Table 3.
[a]At a color Doppler scale between 40 and 60 cm/s. Note that some studies suggest an average VCW of >9 mm should define severe TR.
[b]Color Doppler Nyquist shift down toward 20 cm/s, until the hemispherical flow convergence zone is clearly visualized.
[c]Unless other reason for flow reversal (ie, atrial fibrillation, right atrial elevated pressures/noncompliance). Adapted from: 1) Zoghbi et al[16]; 2) Lancellotti et al[8]; and 3) Hahn et al.[19]

T-TEER.[55] Echocardiography estimates of PA systolic pressure correlate well with invasive measurement in patients with nonsevere TR, but may underestimate PA systolic pressure when there is rapid equilibration of RA and RV pressures, which may occur with severe TR with or without a noncompliant RA.

Recent PH guidelines recommend confirmation of PA pressures with invasive right heart catheterization.[56] The routine assessment of invasive pulmonary vascular hemodynamics in patients with TR is even more important given the discordance that may occur in some patients with severe disease. A recent study showed that high PA pressures by invasive measurement with discordant low estimated pressures by echocardiography is associated with poor outcomes following T-TEER.[57] Variables that should be obtained by right heart catheterization are listed in Supplemental Table 4. The pulmonary artery pulsatility index, defined as the ratio of PA pulse pressure to RA pressure, has

emerged as a predictor of RV failure and worse survival in patients with moderate or greater TR without pulmonary hypertension.[58]

Because of the sensitivity of the RV to afterload, an index of ventricular contractility to afterload may further characterize RV function compensation to specific loading conditions. RV-PA coupling describes a hemodynamic state where mechanical stroke work is most efficiently transferred to the pulmonary vasculature, whereas uncoupling suggests the RV can no longer maintain forward cardiac output.[59] Multiple noninvasive measures of RV function have been coupled to estimates of PA pressure; however, TAPSE/systolic pulmonary artery pressure (sPAP) has been the most frequently studied. In contrast to TAPSE[60] or sPAP alone,[61] TAPSE/sPAP is associated with outcomes among patients undergoing transcatheter TV repair.[57,62] Thus, despite the inaccuracies of sPAP measurements in some patients with TR, these studies suggest that TAPSE/sPAP by echocardiography may predict
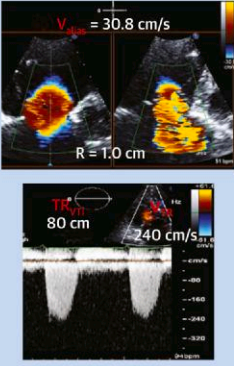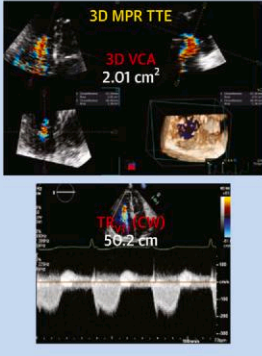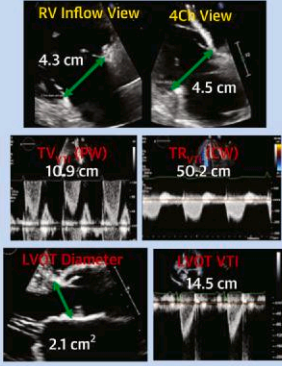
Figure 2 Echocardiographic Quantitative Measures of TR Severity

Assessment of tricuspid regurgitation (TR) severity includes quantitative assessment of regurgitant orifice area (EROA), regurgitant volume (RegVol) and regurgitant fraction (RegFraction). Three methods of quantitation include: proximal isovelocity surface area (PISA) method, planimetry of the 3-dimensional vena contracta area (3D VCA), and quantitative Doppler method. The last method is not used clinically at this time, but allows quantitation of RegFraction as RegVol/Diastolic SV, because diastolic SV should equal the total right ventricular (RV) SV. Investigators have also used 3D echocardiography to quantify total RV SV. CW = continuous wave; LVOT = left ventricular outflow tract; PW = pulsed wave; SV = stroke volume; TTE = transthoracic echocardiogram; VTI = velocity time integral.

outcomes. The use of invasively measured sPAP in assessing RV-PA coupling may have additional predictive benefit.[63] Another estimate of RV-PA coupling is RV stroke volume indexed to RV end-systolic volume, whether measured by computed tomography[64] or by 3-dimensional echocardiography.[65] The latter method avoids the use of echocardiographic estimates of sPAP. Which measures and what cut-offs of RV function should be used to determine a patient's suitability for surgical or transcatheter therapy is unknown.

Current treatment options for TR
Medical therapy for right heart failure secondary to TR

There is limited data to define appropriate medical therapy for TR, with no Class I recommendations in current guidelines.[13,25] The use of diuretic agents is a Class IIa recommendation in the current American College of Cardiology/American Heart Association valve guidelines, but robust clinical trial evidence is lacking.[13,66–68] An understanding of renal physiology and diuretic pharmacokinetics is essential to the thoughtful use of diuretic agents in the management of heart failure. According to the recent position statement of the European Society of Cardiology,[67] diuretic response should always be interpreted considering the dose and type of the diuretic agent administered (*Supplemental Table 5*) and the degree of volume overload, body composition, and kidney function. Loop diuretic agents are recommended in chronic heart failure to prevent signs and symptoms of congestion; however, these drugs must be secreted into the proximal convoluted tubule requiring adequate dosing with sufficient plasma levels. Thiazide and thiazide-like diuretic agents and sodium-glucose cotransporter-2 inhibitors may offer an additional therapeutic option because of their diuretic effects. Other diuretic agents are listed in *Supplemental Table 5*.

Besides the effects of reduced renal perfusion and changes in pharmacokinetics, diuretic resistance occurs in the late-stages of right heart failure caused by multiple neurohormonal changes and reduced intestinal absorption. European guidelines suggest a stepped pharmacologic approach focused on achieving successful decongestion with alterations in diuretic therapy based on frequent treatment reassessment.[67] Notwithstanding these guidelines, medical therapy remains a significant challenge in the presence of diuretic resistance, variable renal function, and associated electrolyte disturbances. Because of the vicious cycle of TR begetting more TR (*Figure 3*), the goals of optimal medical therapy should likely be the same as the goal of interventional therapy, which is to reduce TR to mild or less.
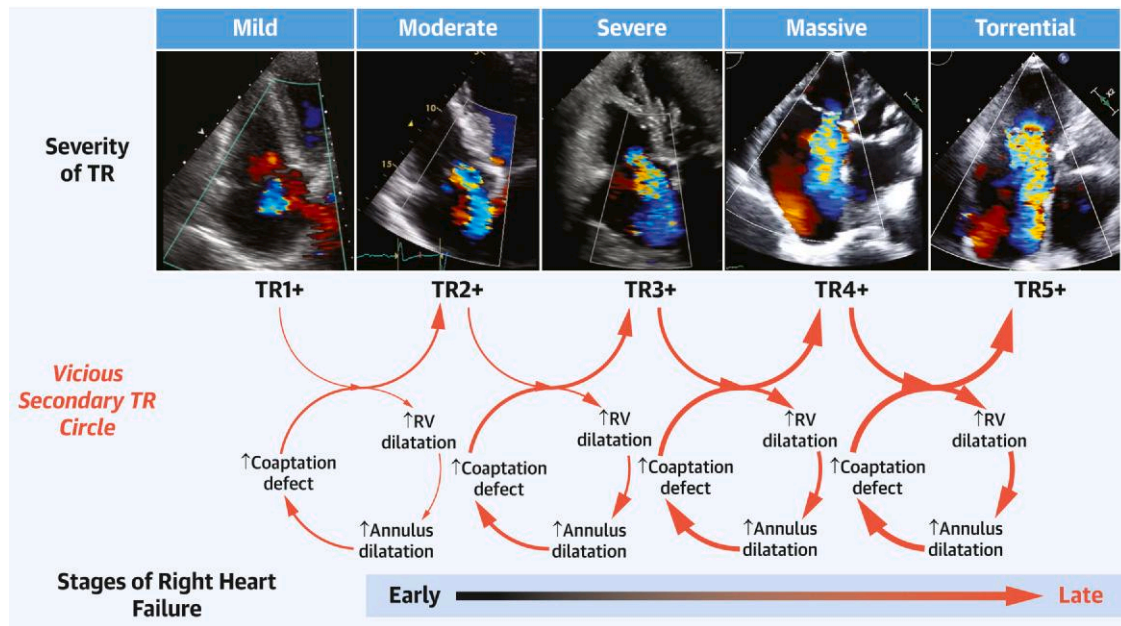
Figure 3 Progression of TR and Right Heart Failure

Tricuspid regurgitation (TR) of any etiology results in maladaptive dilatation of the right ventricle, which can subsequently result in further annular dilatation and tethering of the leaflets. A vicious cycle then ensues until, late in the disease, the reduced cardiac output results in signs and symptoms of right heart failure.

Current valve guidelines also state that the primary cause of heart failure should be treated (eg, pulmonary vasodilators to reduced elevated PA pressures, guideline-directed medical therapy for heart failure with reduced or preserved left ventricular ejection fraction, or rhythm control of atrial fibrillation).[13,25,68,69] Optimal medical and device therapy for left heart failure should follow published guidelines[68,70] and consensus documents.[71] Importantly, all medical therapies should be recorded at baseline and after management changes (*Supplemental Table 6*), to improve our understanding of the role of medical therapy in the management of patients with TR.

Outcomes of surgical therapies for TR

A referral for surgical or percutaneous intervention has often been delayed until significant signs or symptoms of advanced stages of right heart failure occur. In addition to poor RV function, right heart failure is associated with worse outcomes after isolated TV surgery.[72] In addition, comorbidities, advanced heart failure, rapid equalization of RV to RA gradients,[73] and large systolic RV areas[74] have been identified as independent predictors of poor outcome. Thus, in-hospital mortality for isolated TR has been as high as 9% to 11% with a morbidity rate of ~30%.[75] Consequently, utilization of surgery remains low compared with the prevalence of TR.[76] Dedicated surgical risk scores have only recently been described,[72,77] with other studies finding utility in the use of standard surgical risk scores or hepatorenal scores[78] (*Supplemental Table 7*). All surgical risk scores require further validation.

Outcomes of transcatheter therapies for TR

Given the constantly evolving landscape for TTVI devices (*Figure 4*), specific devices will not be discussed individually. Current clinical trials are listed in *Supplemental Table 8*. A propensity-matched registry study showed an improvement in survival and heart failure hospitalizations in patients treated with TTVI compared with medical therapy.[79] The

recent report from the Triluminate Pivotal Trial demonstrated an improved outcome in the composite endpoint after TTVI, which was driven by an improvement in quality of life.[24] However, the study failed to show a benefit in mortality and heart failure hospitalizations over medical therapy. The rates for preceding heart failure hospitalizations and the observed rates for 1-year mortality in both arms were very low (~10%), and further analysis in the patient population is warranted.

The impact of TTVI on RV function is unclear so far. Multiple studies have, however, shown no significant acute changes in RV function following T-TEER,[80,81] or even short-term improvement.[82] A meta-analysis of TTVI studies shows that in the setting of TR reduction following TTVI, a reduction in RV function may nonetheless be associated with an improvement in cardiac output.[39]

Section 2: endpoint definitions

Inherent in any discussion of endpoint definitions is the timing and duration of follow-up for each endpoint. Duration of follow-up should be long enough to allow reliable ascertainment of the effectiveness and safety of TR therapy. The timing of endpoint assessment must be considered when interpreting the periprocedural and the early and late risks and benefits of the TR therapy (*Table 8*). At a minimum, the occurrence of clinical outcomes should be reported in-hospital, at 30 days, and at 1 year. Common safety endpoints are frequent at the in-hospital and 30-day time points, while less common safety endpoints and device failures may be identified during longer follow-up. Premarket studies should continue follow-up through 5 years, as for other implantable devices. Imaging efficacy endpoints should be reported at postprocedure or predischarge, 30 days, and 1 year at minimum, and yearly up to 5 years in premarket studies. Powered clinical efficacy endpoints may be best assessed at a minimum of 1-year follow-up. Finally, the duration of follow-up must be sufficient to ascertain whether device durability is

Table 5 Echocardiographic Assessment of Right Ventricular Function

	Mean ± SD	Lower Limit of Normal
Longitudinal systolic function		
TAPSE, mm	21.8 ± 3.8	15.2
RV TDIs'	13.2 ± 2.3	9.4
RV GLS, |%|	25.4 ± 3.8	18.2
RVFWS, |%|	28.3 ± 4.3	20.0
Circumferential systolic function		
RV FAC, %	42.8 ± 4.3	35.3
RVEF (3D echo), %	56 ± 6	44
Systolic and diastolic function		
RIMP (PW Doppler)	0.25 ± 0.085	0.0
RIMP (TDI)	0.38 ± 0.08	0.22

Adapted with permission from Addetia et al[14] and Addetia et al.[15]
FWS = free wall strain; GLS = global longitudinal strain; PW = pulsed wave; RIMP = right ventricular index of myocardial performance; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; other abbreviations as in *Table 3*.

Table 6 Echocardiographic Assessment of Right Ventricular Size

RV Size Parameter	Mean ± SD	Upper Limit of Normal
RV apical focused view		
RV basal diameter, mm	32.8 ± 5.3	44.2
RV basal diameter index, mm/m^2	18.6 ± 2.7	24.5
RV mid diameter, mm	26.4 ± 5.7	38.6
RV mid diameter index, mm/m^2	15.0 ± 2.9	20.9
RV length (4Ch view), mm	73.7 ± 8.7	91.8
RV length index, mm/m^2	41.9 ± 5.1	52.5
Parasternal view		
RVOT PLAX diameter, mm	27.9 ± 4.2	36.4
RVOT PLAX diameter index, mm/m^2	15.8 ± 2.3	20.8
RVOT PSAX proximal diameter, mm	28.3 ± 4.9	38.1
RVOT PSAX proximal diameter index, mm/m^2	16.1 ± 2.8	22.1
Tricuspid annulus, mm	28.6 ± 5.1	39.4
Tricuspid annulus index, mm/m^2	16.4 ± 2.6	22.0
Subcostal RV wall thickness, mm	3 ± 1	1–5
RV volume		
RV EDV, mL	137 ± 44	179
RV EDVi, mL/m^2	76 ± 20	95
RV ESV, mL	61 ± 22	84
RV ESV, mL	76 ± 24	43
RV ESVi, mL/m^2	34 ± 11	37

Adapted with permission from Lang et al,[53] Addetia et al,[14] and Addetia et al.[15]
4Ch = 4-chamber view; EDV = end-diastolic volume; EDVi = end-diastolic volume indexed to body surface area; ESV = end-systolic volume; ESVi = end-systolic volume indexed to body surface area; RV = right ventricle; RVOT = right ventricular outflow tract; PLAX = parasternal long-axis; PSAX = parasternal short-axis view.

acceptable for the intended patient population and comparable to alternative therapies.

1. Efficacy endpoints: clinical, patient-centered, and surrogate outcomes

All-cause and cardiovascular mortality

Although cardiovascular mortality is an important contributor to total mortality in TR, differentiating between cardiovascular and noncardiovascular mortality may be challenging in TR patients, because right heart failure is often accompanied by cardiorenal and cardiohepatic syndromes. It is therefore recommended that all-cause mortality is used as the primary mortality endpoint in TR therapy trials.

Cardiovascular mortality can be adjudicated as a secondary endpoint given the previously mentioned considerations and subcategorized as indicated in *Table 9*. Noncardiovascular mortality is adjudicated only as a death clearly related to a noncardiovascular cause. Procedure or device relatedness should be ascertained in view of existing recommendations.[83] In TR trials, relatedness to TR for both cardiovascular and noncardiovascular deaths (eg, hepatic failure, endocarditis) must also be ascertained.

Hospitalization endpoints

TR and right heart failure are associated with a high hospitalization rate. As per the Heart Failure Collaboratory and Academic Research Consortium,[71] trials should report both all-cause hospitalizations as well as cardiovascular and heart failure hospitalizations (*Table 10*). Hospitalizations should also be adjudicated as valve (both native or device) and/or procedure-related. Particularly in the COVID-19 era, it should be recognized that heart failure may be treated more aggressively in the outpatient setting (including ED visits) with either intravenous or more intense oral diuretics. In the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial such "heart failure

hospitalization equivalent" events had similar prognostic implications for both total and cardiovascular mortality as traditional inpatient hospitalizations.[84] Including these events as heart failure events controls for variability between sites in threshold for hospitalization and increases the power of studies by increasing the number of events.

Patient-centered outcomes

Disease-state comparisons and endpoint definitions

The optimization of a patient's health status (ie, symptoms, functional status, and quality of life) is a central goal in the treatment of disease. Accordingly, patient-reported outcomes measures are being incorporated more frequently into the assessment of new devices, and the U.S. Food and Drug Administration has recognized that a treatment may demonstrate effectiveness based on improvement in health status alone[85] (*Supplemental Table 9*).

Disease-specific assessment of health status

Disease-specific measures are designed to evaluate the effects of a specific disease process on health status. The most commonly used disease-specific instruments for patients with heart failure include the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire. KCCQ changes of 5, 10, and 20 points represent small, moderate, and large improvements in a patient's quality of life.[86] Unfortunately, the placebo effect in unblinded as well as sham-control trials remains a major pitfall for this measurement, with up to 10- to 12-point improvements seen in the control arms of heart failure trials.[87] The novel design of the Triluminate Pivotal trial included KCCQ as a coprimary composite endpoint along with mortality or TV intervention, and heart failure hospitalization; only KCCQ showed a significant difference between treatment groups.[24] A ≥15-point increase in KCCQ (considered significant) was reached in patients with moderate or less TR at 1 year.[24] Importantly, to attribute a change in patient symptoms to TR reduction, patients should be on a stable medical regimen before and following device therapy. Increasing diuretic agents in the "control" group, as was seen in the Triluminate Pivotal trial, as well as increasing diuretic agents just before transcatheter device, which has been an approach to management suggested by some investigators,[82,88] result in differences in "treatment" between the groups that will confound results of device therapy.

Generic assessment of health status

In contrast to disease-specific measures, generic health status measures are designed to be used in patients with any disease or condition, thereby allowing for comparisons across disease states.

Other assessments of functional capacity

In addition to measuring a patient's perception of their functional status and quality of life, objective performance measures (which are not true

Table 7 Proposed Echocardiographic Cutoffs for Right Ventricular Function for Clinical Trials

	Mild Dysfunction	Moderate Dysfunction	Severe Dysfunction
TAPSE, mm	14–17	10–13	<10
RV TDIs', cm/s	9–11	6–8	<6
RV GLS, |%|[a]	18–21	14–17	<14
RV FWS, |%|[a]	20–23	15–19	< 15
FAC, %[b]	34–37	30–33	<30
RVEF (3DE), %	45–50	35–45	<35

3DE = 3-dimensional echocardiography; other abbreviations as in Tables 3 and 5.
[a]From Ancona F, Melillo F, Calvo F, et al. Right ventricular systolic function in severe tricuspid regurgitation: prognostic relevance of longitudinal strain. *Eur Heart J Cardiovasc Imaging*. 2021;22(8):868–875.
[b]From Anavekar NS, Skali H, Bourgoun M, et al. Usefulness of right ventricular fractional area change to predict death, heart failure, and stroke following myocardial infarction (from the VALIANT ECHO Study). *Am J Cardiol*. 2008;101(5):607–612.

Figure 4 Transcatheter Tricuspid Valve Investigational Device

In this snapshot of the landscape of transcatheter device therapy, the 4 classic anchoring mechanisms are listed in the **left column** with examples of devices in each **row**. Devices of historical interest **(red outline),** devices in early human use **(blue outline),** devices in early feasibility studies **(purple outline),** and devices in randomized controlled trials **(green outline)** are shown. Of note, devices with a **star** have received the Conformité Européenne (CE) mark in Europe. IVC = inferior vena cava; SVC = superior vena cava.

Table 8   Timing of Events With Respect to Procedure

Type	Definition
Periprocedural	≤30 d or before discharge (whichever comes last) after a procedure
Acute	<24 h from index procedure
Subacute	≥24 h and ≤30 d
Early	>30 d but ≤1 y after index hospitalization
Late	>1 y after index hospitalization

Table 9   Mortality Endpoints

All-Cause Mortality	Cardiovascular Mortality and Noncardiovascular Mortality
Cardiovascular mortality	Death classified and adjudicated as 1 of the mutually exclusive categories below:
	Cardiac mortality—death related to:
	• Heart failure
	• Cardiogenic shock
	• Arrhythmia or conduction system disturbances
	• Myocardial infarction
	• Endocarditis
	• Sudden death including unwitnessed death
	• Death of unknown cause
	Vascular mortality—death caused by noncardiac vascular causes classified and adjudicated as one category below
	• Cerebrovascular disease/stroke
	• Pulmonary embolism
	• Noncerebral thromboembolism
	• Vascular bleeding
	• Tamponade
	• Ruptured aortic aneurysm
	• Dissecting aneurysm
	• Vascular complications including infection
	Valve-related mortality[a]—death presumed to be related to
	• Device/valve dysfunction/failure
	• Device/valve-related periprocedural mortality[b]
	• Unplanned intervention (eg, surgical or transcatheter procedure) performed to correct device/valve dysfunction/failure
	Cardiohepatic: hepatic failure related to tricuspid valve dysfunction
	Cardiorenal: renal failure related to tricuspid valve dysfunction
Noncardiovascular mortality	Death clearly related to a noncardiovascular cause such as respiratory failure not related to heart failure (eg, pneumonia), noncardiac renal failure, noncardiac liver failure, infection (eg, urosepsis), cancer, trauma, and suicide

[a]Relatedness to device therapy should be adjudicated for each endpoint.
[b]Timing with respect to device therapy to be classified as per *Table 8*.

patient-reported outcomes) can also be used to further quantify a patient's physical function and health status. The most commonly used measure is the 6-minute walk test (6MWT), which can be affected by age and sex.[89] In general, a 25- to 50-m increase in the 6MWT is considered a clinically significant improvement for an individual patient, although these thresholds may vary for patients with differing functional levels at baseline.[90,91]

Although the 6MWT provides clinicians with a snapshot of a patient's abilities, this assessment may not reflect a patient's usual activities at home. Continuous actigraphy may allow for a more complete assessment of a patient's functional status.[92] Actigraphy involves use of a wearable accelerometer to measure acceleration along multiple axes and can be used to estimate energy expenditure based on validated algorithms.

Imaging endpoints
Reduction of TR and absence of TS
Comprehensive echocardiography, using a multiparametric approach but relying on quantitative measures, remains the test of choice in preprocedural and postprocedural TR grading.[93] Imaging endpoints followed serially from baseline to 5 years postintervention for TV repair or replacement in early feasibility and pivotal clinical trials are best assessed via 2- and 3-dimensional echocardiography given its broad availability. CMR imaging is an acceptable alternative for quantification of TR severity given recent data on prognostication with using CMR parameters, although it may have different severity cutoffs.[33] All measures of TR severity are more robust in the setting of isolated disease and are limited by the absence of a true gold standard and the dynamic nature of TR severity in terms of both volume status and beat-to-beat variation with respiration or arrhythmia/atrial fibrillation.

The assessment of postdevice TR currently relies predominantly on TTE, based on integration of information from qualitative and semiquantitative parameters of color and spectral Doppler. The type of device significantly affects the utility of particular parameters for TR assessment (*Table 11*). The multiple residual regurgitant jets following T-TEER and deformation of the proximal flow convergence by the device limit the applicability of semiquantitative and quantitative measures of severity.[94] Nonetheless, moderate or more (≥2+) residual TR following device therapy is associated with adverse outcomes.[39,95] Given the pitfalls of postdevice quantitative methods depending on device type, 3D-VCA may be an important method for assessing both baseline and postdevice efficacy; however, significant limitations of this method also exist. Precise algorithms to integrate discordant parameters need to be developed and validated. Ongoing advances in echocardiographic platforms and automation of quantitation should improve the quantification of both TR severity and RV function.

Continuous wave Doppler measurements to assess for TS include pressure half-time, peak and mean transtricuspid diastolic gradients, peak and mean transtricuspid systolic (eg, regurgitant) gradients, and the diastolic VTI. The left ventricular outflow VTI should also be

Table 10   Hospitalization Endpoints

All-cause hospitalization	Hospitalization is defined as an unplanned admission to an inpatient unit or ward in the hospital for ≥24 h or as measured by a change in calendar date, including an emergency department stay. Preplanned hospitalizations for pre-existing conditions or for planned procedures are excluded unless theses are arranged for a condition related to the tricuspid valve dysfunction such as worsening heart failure.

Cardiovascular hospitalization	Heart failure hospitalization
	
	• *Heart failure–related hospitalizations* requiring that new or worsening heart failure be the predominant reason for a hospital stay >24 h on the basis of symptoms and signs of heart failure with confirmation by diagnostic tests and necessitating treatment using intravenous or mechanical heart failure therapies. Note: Pleural effusions requiring medical or interventional therapy >24 h but within 4 weeks of surgical intervention, not associated with new postprocedural valvular or ventricular dysfunction, are not considered a heart failure complication or a heart failure hospitalization equivalent.
	• **Both** of the following additional criteria are present:
	  (1) At least 1 symptom and 2 physical findings or 1 physical finding and at least 1 laboratory or invasively measured criterion (if measured within 24 h of admission) all of which are new or worsening
	  (2) Administration of intravenous, intensification of oral, or mechanical heart failure therapy
	
	Other cardiovascular hospitalization
	
	• *Cardiovascular hospitalization not directly related to the valve or index procedure* including: acute coronary syndrome or chronic coronary syndrome, hypertension, arrhythmia (not related to the procedure or tricuspid valve), peripheral vascular disease.
	
	Valve- or procedure-related hospitalization
	
	• *Device-related dysfunction* such as single leaflet attachment, device embolization, arrhythmias, and so on
	• *Exacerbation or deterioration of previous in-hospital periprocedural complication*
	• *Untreated tricuspid valve disease*
	• *Bioprosthetic valve dysfunction* such as valve thrombosis, endocarditis, structural valve deterioration, or nonstructural valve dysfunction
	• *Bleeding complications related to oral anticoagulation or antiplatelet therapy* for valve-related thromboembolic prevention or atrial fibrillation
	
	Unknown
	
	• *Hospitalizations from unknown causes and not clearly cardiovascular or noncardiovascular*

Noncardiovascular hospitalization	Noncardiovascular hospitalization - Hospitalization not caused by cardiovascular causes as listed in the previous text

Heart failure exacerbation	Heart failure exacerbation without hospitalization
	
	• The patient experiences signs and symptoms of new or worsening heart failure and is seen in a clinic, emergency department, or observational unit but does not require hospitalization and the stay is <24 h.
	• **Both** of the following additional criteria are present:
	  (1) At least 1 symptom and 2 physical findings or 1 physical finding and at least 1 laboratory or invasively measured criterion (if measured within 24 h of admission) all of which are new or worsening
	  (2) Administration of intravenous or intense oral heart failure therapy is administered

Relatedness to device therapy should be adjudicated for each endpoint. Timing with respect to device therapy to be classified as per *Table 8*.

measured to calculate the Doppler velocity (or VTI) index. Current normal hemodynamic performance values for surgical bioprosthetic and mechanical prosthetic valve are listed in *Supplemental Table 10*, which may inform shared decision making when considering surgical or transcatheter replacement options. If TS is suspected after TV replacement, leaflet excursion, thickening, and valve area can be assessed by 4-dimensional transesophageal echocardiography or full-cycle CT imaging to confirm whether the valve is functioning normally or whether there is evidence of leaflet thrombus or restriction.

Cardiac output

Multiple transcatheter TV therapy studies have reported an increase in stroke volume and cardiac output, presumably caused by reduction in TR.[21,22,60,96] Cardiac output should be measured at baseline and

following TTVI using invasive or noninvasive (echocardiography, inert gas rebreathing spirometry, or CMR) methods.

Hepatic vein flow reversal

Hepatic vein flow reversal is a specific sign of clinically significant TR,[16] which in the original studies, included both moderate and severe disease. Hepatic vein flow reversal may be affected by not only TR, but also by RA chamber compliance, and peak TR pressure gradients.

RV function and RV-PA coupling

Noninvasive parameters of RV function are inherently load-dependent, and, in conditions of altered preload and/or afterload or regional RV dysfunction, may not provide an accurate representation of RV intrinsic or overall performance. Nonetheless, these measurements have been

Table 11   Echocardiographic Parameters for Assessing TR Severity Pre- and Post-TTVR

	Baseline	Post-TEER	Post-Annular Repair	Post-TTVR (Orthotopic)
Qualitative parameters				
Flow convergence zone	+	+	+	+
CWD jet density/shape	+	+	+	+
Semiquantitative parameters				
Color flow jet area	++	+	+	+
VC width (average of orthogonal views)	+++	+ (adding multiple jets has not been validated)	+++	+++
PISA radius	+++	± (abnormal shape of proximal flow may result in overestimation)	+++	+++ (for central TR)
Hepatic vein flow pattern	++	± (abnormal RA compliance may affect specificity)	± (abnormal RA compliance may affect specificity)	± (abnormal RA compliance may affect specificity)
Quantitative parameters				
PISA EROA	+++	± (abnormal shape of proximal flow may result in overestimation)	+	+++ (for central TR)
2D Doppler quantitative EROA	++	-	+	-
3D vena contracta area	+++	+++	+++	+++
Regurgitant volume	+++	+	+	+
Regurgitant fraction	+++	(+)[a]	+++	(+)[a]

PISA = proximal isovelocity surface area; VC = vena contracta; other abbreviations as in *Tables 3* and *4*.

[a]Given the diastolic flow restriction by the device, diastolic stroke volume will be overestimated. Regurgitant fraction may be performed if a total RV stroke volume is obtained by other methods (ie, 3D echocardiography or cardiac magnetic resonance) and regurgitant volume is quantified by 3D VCA. + indicates the utility of the parameter with multiple plus signs indicating greater utility; − indicates no utility or significant limitations of the parameter; ± indicates possible utility.

associated with outcomes for native TR postsurgical and post-TTVI, and thus should be reported. The quantification of RV-PA coupling provide important insights into the mechanism of adaptation of RV contractility to afterload in patients with TR.[97] In addition to noninvasive measures of RV afterload, invasively measured PA pressures (systolic, diastolic, and mean) as well as pulmonary capillary wedge pressures, pulmonary vascular resistance, and transpulmonary gradients allow differentiation of precapillary, postcapillary, and combined precapillary and postcapillary PH. The differentiation of these entities may determine the most appropriate medical and transcatheter therapies.

RV/RA reverse remodeling after TV intervention

The effects of transcatheter TV repair procedures on the RV and RA size and function remain to be clarified. Available studies have reported conflicting results in terms of RV and RA size reduction and RV function improvement.[39] Current trials should routinely report measures of right heart size and function during follow-up.

Circulating biomarkers and end-organ function

Although there has been extensive research to identify, characterize, and determine the prognostic significance of biomarkers related to left-sided heart disease and failure, comparatively little data is available for the right heart and more specifically for TR. Significant TR produces volume overload of the RV, causing stretch and stress of the myocardium with an accompanying release of cardiac proteins, most notably natriuretic peptides.[98–100] Although circulating natriuretic peptide levels tend to be

more influenced by left-sided cardiac disease, ventricular interdependence results in elevations of these markers in the setting of right heart failure. Natriuretic peptide levels have been shown to be predictors of outcomes in primary PH,[101,102] and a reduction in septal shift may improve left heart function and reduce pulmonary congestion. Because congestion is a dominant feature of right-sided heart failure associated with significant TR, CA125 may turn out to be a useful biomarker responsive to reductions in TR.[103,104] Liver and renal function are also linked to the venous congestion and reduced forward flow associated with significant TR. Accordingly, circulating markers of liver and renal function may respond to treatment of TR, particularly if they are abnormal before the procedure.[105] To identify and evaluate known and novel biomarkers of procedural success and predictors of clinical outcome, it will be helpful to include biobanks in trials testing TV therapies. It should be noted that their association with TR severity, responsiveness to reduction in TR, and clinical outcomes are currently unknown. *Table 12* outlines the circulating biomarkers that should be routinely included in TR trials.

2. Safety endpoints, including device-related complications and success endpoints

Safety endpoints

TV reintervention

A repeat intervention for TV disease is defined as a transcatheter or surgical procedure that targets new-onset or persistent valve or device

Table 12 **Circulating Biomarkers and End-Organ Function**

Biobanks	Recommended for inclusion in trials testing therapies for TR to identify and characterize the association between known and novel circulating biomarkers and procedural success and longer-term clinical outcomes
Cardiac	N-terminal pro-hormone B-type natriuretic peptide
Renal	BUN
	Creatinine
	eGFR
Liver	Albumin
	Transaminases (AST, ALT)
	Alkaline phosphatase
	Gamma-glutamyl transferase (GGT)
	Bilirubin
	INR
	MELD score (requires creatinine, bilirubin, INR, sodium)
Hematologic	WBC (with differential)
	Hemoglobin and hematocrit
	Platelets

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; INR = international normalized ratio; MELD = model for end-stage liver disease; WBC = white blood cell.

dysfunction following a prior TV procedure. To be classified as a safety endpoint, reinterventions should be unplanned (ie, planned staged interventions are excluded) and may be related to a prior unsuccessful procedure, a device-related complication, either acute (eg, embolization) or chronic (eg, paravalvular leak) events, or device failure. Device explants should be classified as reinterventions as well. Transcatheter or surgical procedures targeting procedural complications should also be noted as safety endpoints.

Bleeding

Bleeding is a central safety outcome in cardiovascular trials and can be challenging to ascertain and grade. The use of consistent standardized bleeding scales across different types of cardiovascular studies will avoid confusion among clinicians and investigators and facilitate comparison of bleeding risk across patient population and procedure types. TVARC has therefore aligned its bleeding endpoints with the Bleeding Academic Research Consortium scale,[106] which has become widely used in cardiovascular trials (*Table 13*).

Vascular, access-related, and cardiac injury

Table 14 shows definitions and severity of vascular, nonvascular access, and cardiac injury complications. TVARC leverages prior definitions from MVARC (Mitral Valve Academic Research Consortium) and VARC-3 (Valve Academic Research Consortium 3), with minor differences derived from the point of access (eg, venous vs arterial) and cardiac chamber involvement (eg, right-sided vs left-sided structures).

Table 13 **TVARC Bleeding Classification**

Type 1
- Overt bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional

Type 2
- Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least 1 of the following criteria: 1) requiring nonsurgical, medical intervention by a health care professional; 2) leading to hospitalization or increased level of care; or 3) prompting evaluation

Type 3

Type 3a
- Overt bleeding plus hemoglobin drop of 3 to <5 g/dL[a] (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b
- Overt bleeding plus hemoglobin drop ≥5 g/dL[a] (provided hemoglobin drop is related to bleed)
- Cardiac tamponade caused by bleeding into the pericardial space
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c
- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4: Thoracotomy or percutaneous entry-site related bleeding
- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of entry site for the purpose of controlling bleeding
- Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period[b]
- Chest tube output ≥ 2 L within a 24-h period

Type 5: Life-threatening bleeding

Type 5a
- Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
- Type 5b
- Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

[a]Corrected for transfusion (1-U packed red blood cells or 1-U whole blood = 1 g/dL hemoglobin).
[b]Cell saver products are not counted. Adapted with permission from the Bleeding Academic Research Consortium.[106]

Conduction disturbances and complications involving CIEDs

Preprocedural and postprocedural conduction disturbances, and the resultant need for ventricular pacing, are key considerations in the management of TR. Postprocedural conduction disturbances are frequently observed following surgical TV intervention.[46] In early feasibility studies,

Table 14 Vascular, Nonvascular Access, and Cardiac Complications

Vascular complications

Definitions
- Access-site related venous or arterial injury (dissection, stenosis, perforation, rupture, thrombosis, arteriovenous fistula, pseudoaneurysm, hematoma, compartment syndrome, or infection)
- Distal embolization (noncerebral) from a vascular source
- Unplanned endovascular or surgical intervention
- Closure device failure

Severity
- Major: resulting in death, TVARC type ≥ 3 bleeding, limb or visceral ischemia, amputation, or irreversible end-organ or neurological impairment
- Minor: not resulting in death, TVARC type ≥ 3 bleeding, limb or visceral ischemia, amputation, or irreversible end-organ or neurological impairment

Nonvascular access complications

Definition
- Nonvascular access site (eg, right ventricular apex) or nonvascular, noncardiac structure perforation, injury, or infection

Severity
- Major: resulting in death, TVARC type ≥ 3 bleeding, irreversible nerve injury, or requiring unplanned surgery or percutaneous intervention
- Minor: not resulting in death, TVARC type ≥ 3 bleeding, irreversible nerve injury, or requiring unplanned surgery or percutaneous intervention

Cardiac complications

Definitions
- Cardiac structure perforation, injury, or compromise including but not limited to:
  - Tricuspid valve/leaflet (eg, perforation, tear, restriction, or impingement)
  - Tricuspid annulus/periannular structures (eg, disruption, perforation, or distortion resulting in hemodynamic compromise, AV conduction disturbance)
  - Right atrium or vena cavae (eg, perforation, aorto-atrial fistula, atrial septal injury)
  - Right ventricle (eg, perforation, pseudoaneurysm, papillary muscle disruption, pulmonic valve injury)
- New pericardial effusion
- Coronary arterial partial or total occlusion, ischemia
  - Includes coronary perforation in setting of annular reduction

Severity
- Major: resulting in death, TVARC type ≥ 3 bleeding, myocardial infarction, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
- Minor: not resulting in death, TVARC type ≥ 3 bleeding, myocardial infarction, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention

Adapted with permission from VARC-3 (Valve Academic Research Consortium 3).[110]
AV = atrioventricular.

pacemaker rates following transcatheter TV intervention appear to be low following T-TEER and annuloplasty repair,[21,22,82,107] but are at least 11% following transcatheter TV replacement.[108] In patients at high risk of postprocedural conduction system disturbance, preprocedural planning for potential pacing strategies, including His-bundle, left bundle, coronary sinus, and leadless RV pacing, should be considered as part of a heart team approach. Table 15 presents an adaptation of conduction-related disturbances from VARC-3 that considers adverse effects of the procedure on the conduction system as well as on pre-existing CIEDs.

Neurological events

Although less frequent than in left heart interventions, neurological events may still occur because of paradoxical emboli in the presence of patent foramen ovale or other intracardiac shunts, as well as in the setting of periprocedural hemodynamic compromise. TVARC leverages neurological event definitions from NeuroARC and VARC-3 in Table 16, which are recommended for adjudication of cerebrovascular events in tricuspid intervention trials.

Pulmonary embolism and deep vein thrombosis

Large-bore venous access and right-sided device therapy predispose patients undergoing TTVI to venous thromboembolic complications. TVARC identifies pulmonary embolism and deep vein thrombosis as 2 events that require careful ascertainment and reporting in tricuspid trials. For standardization, TVARC proposes definitions of these outcomes, as well as for right atrium/right ventricle thrombus, which are summarized in Table 17, including a proposed classification based on severity and clinical relevance.

Acute kidney injury

The rate of newly initiated renal replacement therapy appears to be infrequent in early feasibility studies following transcatheter device therapies for TR.[82,107–109] TVARC recommends assessing chronic kidney disease according to the definitions in the Heart Failure Collaboratory and Academic Research Consortium[71] (Table 18), TVARC recommends assessing acute kidney injury (AKI) according to KDIGO criteria with the addition of stage 4 AKI, defined as AKI requiring new temporary or permanent renal replacement therapy. The TVARC AKI criteria are consistent with VARC-3.[110] Importantly, reduction in TR with resulting improvement in renal perfusion pressure may be associated with an improvement in renal function.

Device- and procedure-related complications

Defining device-related vs procedure-related complications can be challenging, particularly in the periprocedural setting. For example, device embolization may be the result of a procedural error, but device design itself may be a key contributor. Even events beyond the periprocedural time period may be influenced by procedural events; eg, paravalvular regurgitation may be the result of undersizing of the device. Complications related to device delivery systems should be distinguished from complications related to the transcatheter valve repair or replacement device itself. ARC has recently established general recommendations[83] with regards to cardiovascular device trials. When there is not a clear distinction between device-related vs procedure-related complications, ARC recommends that attribution be assigned to both, with relative probabilities (definitely related, probably related, possibly related, unrelated) helping to define the respective contributions of the device and procedure. In procedures where more generic ancillary devices are used (such as off the shelf vascular access devices), complications attributed to those procedures would typically be considered procedure-related but not device-related, because the

Table 15 Rhythm and Conduction Disturbances

Preindex procedure	
Rhythm or conduction disturbance	First-degree AV block
	Second-degree AV block
	Right bundle branch block
	Left bundle branch block
	Left anterior hemiblock
	Left posterior hemiblock
	IVCD with QRS ≥ 120 ms
	Bradycardia (heart rate <60 beats/min) or sick sinus syndrome
	Atrial fibrillation/flutter (indicate whether paroxysmal or persistent, long-standing, or recent)
CIEDs	Type of implanted CIED should be recorded (eg, single chamber, dual chamber, resynchronization therapy, physiological pacing (ie, HIS and left bundle), leadless pacemaker, transvenous, or subcutaneous defibrillator)
	Implantation indication and date (eg, pre-existing or new in planning before tricuspid intervention)
	Pre-existing device revision or extraction (indicate which)
During or after index procedure[a]	
New-onset[b] rhythm or conduction disturbance	First-, second-, third-degree AV block
	Right bundle branch block
	Left bundle branch block[c]
	Left anterior hemiblock[c]
	Left posterior hemiblock[c]
	IVCD with QRS ≥ 120 ms
	Bradycardia (heart rate <60 beats/min) or sick sinus syndrome
	Atrial fibrillation/flutter
	Nonfatal ventricular arrhythmia (indicate nonsustained [<30 s] or sustained [≥ 30 s])
Timing of rhythm or conduction disturbance	Periprocedural: ≤30 d after the index procedure
	Early: > 30 d but ≤1 y after index hospitalization
	Late: > 1 y after index hospitalization
Duration of rhythm or conduction disturbance	Atrial fibrillation or flutter:
	• Paroxysmal: resolved within ≤7 d of onset
	• Persistent: persisting > 7 d
	• Long-standing persistent: continuous atrial fibrillation > 12 mo in duration
	Bradycardia and conduction abnormalities:
	• Transient: resolved within ≤7 d of onset
	• Persistent: persisting > 7 d
	• Permanent: present for > 30 d
New CIED	Indication: atrioventricular block, sick sinus syndrome, ventricular tachycardia or fibrillation, and so on
	Type:
	Pacemaker: single chamber, dual chamber, resynchronization, physiological pacing (ie, His-bundle or left bundle), leadless, epicardial.
	Defibrillator: single, dual, resynchronization
	Location of leads (eg, transannular, intraventricular, epicardial, coronary sinus, extravascular [subcutaneous, substernal, epicardial]).
	Timing: number of days after the index procedure
Pre-existing CIED	Change in pacing capture threshold (≥ 1 V at 0.5 ms)
	Change in pacing lead impedance (increase or decrease of > 200 Ω)
	Change in atrial or ventricular sensing not amenable to reprogramming

Continued

Table 15 *Continued*

Lead dislodgement
Requirement for device revision after the tricuspid intervention
Entrapment of transannular lead by the device

AV = atrioventricular; CIED = cardiac implantable electronic device; ECG = electrocardiogram; IVCD = intraventricular conduction delay.

[a]The calculation of new pacemaker rates should exclude patients with pre-existing pacemaker. The same principle applies to reporting of rates of new conduction disturbances and arrhythmias.

[b]Defined as any arrhythmia or conduction abnormality that was not present at baseline and lasts sufficiently long to be recorded on a 12-lead ECG or at least 30 s on a rhythm strip.

[c]Left-sided conduction disturbances less likely in tricuspid valve procedures.

Table 16 **Categories of Neurological Events**

Overt CNS injury (NeuroARC Type 1)

   All stroke[a]

• *Ischemic stroke*[b] (NeuroARC Type 1a or 1aH)

• Acute onset of focal neurological signs or symptoms conforming to a focal or multifocal vascular territory within the brain, spinal cord, or retina and fulfilling 1 of the following criteria:

   o Signs or symptoms lasting ≥ 24 h or until death, with pathology or neuroimaging evidence of CNS infarction, or absence of other apparent causes

   o Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory[c]

• *Hemorrhagic stroke* (NeuroARC Types 1b or 1c)

• Acute onset of neurological signs or symptoms caused by intracranial bleeding from intracerebral or subarachnoid hemorrhage not caused by trauma

• *Stroke, not otherwise specified* (NeuroARC Type 1d)

• Acute onset of neurological signs or symptoms persisting ≥ 24 h or until death but without sufficient neuroimaging or pathology evidence to be classified

Symptomatic hypoxic-ischemic injury (NeuroARC Type 1e)

• Nonfocal (global) neurological signs or symptoms with diffuse brain, spinal cord, or retinal cell death confirmed by pathology or neuroimaging and attributable to hypotension or hypoxia

Covert CNS injury (NeuroARC Type 2)

Covert CNS infarction[c] or hemorrhage

• Neuroimaging or pathological evidence of CNS focal or multifocal ischemia (NeuroARC Type 2a or 2aH) or hemorrhage (NeuroARC 2b) *without* acute neurological symptoms consistent with the lesion or bleeding location

Neurological dysfunction (acutely symptomatic) without CNS injury (NeuroARC Type 3)

   TIA (NeuroARC Type 3a or 3aH)

• Transient focal neurological signs or symptoms lasting <24 h presumed to be caused by focal brain, spinal cord, or retinal ischemia, but *without* evidence of acute infarction by neuroimaging or pathology, or with no imaging performed

Delirium without CNS injury (NeuroARC Type 3b)

• Transient nonfocal neurological signs or symptoms, typically of variable duration, *without* evidence of infarction on neuroimaging or pathology, or with no imaging performed

Stroke Grading[a]

Acute stroke severity[d]

• *Mild neurological dysfunction:* NIHSS 0–5

• *Moderate neurological dysfunction:* NIHSS 6–14

• *Severe neurological dysfunction:* NIHSS ≥ 15

Stroke disability[e]

• *Fatal stroke:* death resulting from a stroke

• *Stroke with disability:* mRS score of ≥ 2 at 90 d[e] *and* increase of ≥ 1 from prestroke baseline

• *Stroke without disability:* mRS score of 0 (no symptoms) or 1 (able to carry out all usual duties and activities) at 90 d[e] or *no* increase in mRS category from prestroke baseline

[a]In general, all studies should report at a minimum all stroke and stroke disability.

[b]Includes hemorrhagic conversions when ischemic infarction is the primary mechanism.

[c]When central nervous system (CNS) infarction location does not match transient (<24 h) symptoms, the event should be classified as covert CNS infarction (NeuroARC Type 2a) and transient ischemic attack (TIA) (NeuroARC Type 3a), not as an ischemic stroke.

[d]Severity assessment should be performed at the time of stroke diagnosis using the National Institutes of Health Stroke Scale (NIHSS).

[e]Disability assessment using the modified Rankin Scale (mRS) should be performed between 30–90 days, with 90 days being optimal. Reproduced with permission from VARC-3.[110]

Table 17   Venous Thromboembolic Complications

Definitions
- Deep vein thrombosis is the formation of 1 or more new thrombi in at least 1 of the body's large veins, most commonly in the lower limbs (eg, lower leg or calf) evidenced by ultrasound, CT, magnetic resonance imaging, or invasive venography
- Pulmonary embolism is the intravascular migration of a venous thrombus to the pulmonary arterial circulation evidenced by echocardiography, CT, V/Q, or invasive pulmonary angiography
- Right atrial or right ventricular thrombus in situ evidenced by echocardiography, CT, or magnetic resonance imaging

Severity
- Major: resulting in death, hemodynamic instability, limb ischemia, or percutaneous or surgical debulking (ie thrombectomy), or catheter-directed or systemic administration of thrombolytics, or acute mechanical circulatory support (eg right ventricular assist device, venoarterial extracorporeal membrane oxygenation)
- Minor: not meeting any criteria for major severity

CT = computed tomography; V/Q = ventilation/perfusion scan.

Table 18   Definition of Changes in Renal Function in Heart Failure

Chronic Kidney Injury

General definition: abnormal renal function present for > 3 mo

CKD Stage 1
- Normal eGFR ≥ 90 mL/min/1.73 m^2

CKD stage 2
- Mildly decreased eGFR 60–89 mL/min/1.73 m^2

CKD Stage 3a
- Mildly to moderately decreased eGFR 45–59 mL/min/1.73 m^2

CKD Stage 3b
- Moderately to severely decreased eGFR 30–44 mL/min/1.73 m^2

CKD stage 4
- Severely decreased eGFR 15–29 mL/min/1.73 m^2

CKD stage 5
- Kidney failure eGFR < 15 mL/min/1.73 m^2

Acute Kidney Injury

AKI Stage 1

AKI that fulfils at least 1 of the following criteria:
- Increase in serum creatinine ≥ 150%-200% (≥ 1.5–2.0 × increase) within 7 d compared with baseline
- Increase in creatinine to ≥ 25% of baseline or increase ≥ 0.3 mg/dL (≥ 26.4 mmol/L) within 48 h of the index procedure

AKI Stage 2

AKI that fulfils the following criterion:
- Increase in serum creatinine ≥ 200%-300% (≥ 2.0–3.0x increase) within 7 d compared with baseline

AKI Stage 3

AKI that fulfils at least one of the following criteria:
- Increase in serum creatinine ≥ 300% (≥ 3.0 × increase) within 7 d compared with baseline

Continued

Table 18   *Continued*

- Serum creatinine ≥ 4.0 mg/dL (≥ 354 mmol/L) with an acute increase of ≥ 0.5 mg/dL (≥ 44 mmol/L)

  AKI Stage 4

- AKI requiring new temporary or permanent renal replacement therapy

AKI definitions adapted with permission from KDIGO. Clinical Practice Guidelines for Acute Kidney Injury 2012. Accessed August 15, 2023. https://kdigo.org/guidelines/acute-kidney-injury/. After Mullens et al[67] and Abraham et al.[71]
AKI = acute kidney injury; CKD = chronic kidney disease.

assessment of device relatedness applies to the investigational device only.

Device-related complication endpoints may be specific to the device or a group of devices. For example, single leaflet device attachment is relevant only to T-TEER, whereas paravalvular regurgitation is relevant to TV replacement. TVARC has therefore defined device- and procedure-related complications by category of procedure (repair vs replacement, edge to edge vs annuloplasty, and so on) (Table 19). Hypoattenuated leaflet thickening or restricted leaflet motion are well-described complications of transcatheter aortic valve replacement[111] and may be of particular concern for transcatheter TV replacement given the lower pressure right heart hemodynamics as well as the frequency of atrial fibrillation in this patient population.

Adjudication of complications and associated device and procedure relatedness according to the TVARC definitions should ideally be performed by an independent clinical events committee to ensure objectivity and consistency across sites.

Success endpoints

TVARC distinguishes between immediate intraprocedure technical success vs short- and long-term device and/or procedure-related outcomes and valve performance. Specifically, TVARC defines intraprocedural success as successful deployment and adequate immediate performance of the device in the absence of serious complications, and clinical success as the proper positioning of the device with adequate device function and the absence of procedure-related

Table 19   **Device-Related Complications**

Dislodgement/dehiscence

Embolization

Migration from intended location

Partial detachment/dehiscence
• T-TEER: single leaflet device attachment

Device dysfunction

Residual/recurrent tricuspid regurgitation, including central and/or paravalvular regurgitation
• Major: no change or < 1 grade improvement from baseline TR severity, or ≥ 1 grade worsening from postimplantation assessment, or associated with hemolysis, or requiring intervention or surgery
• Minor: mild or moderate regurgitation without clinical significance (ie, hemolysis or worsening right heart failure)

Tricuspid stenosis (mean gradient > 5 mm Hg)

Leaflet thickening, reduced leaflet motion, and leaflet thrombosis

Definitions:
HALT
• Hypo-attenuating thickening in typically meniscal configuration on 1 or more leaflets visually identified on computed tomography (2D multiplanar reconstructions or 3D volume-rendering), with or without reduced leaflet motion (RLM)[a]
• The extent of HALT should be described per leaflet, using a 4-tier grading scale in regard to leaflet involvement along the curvilinear contour, assuming maximum involvement at the base of the leaflet[111]:
   ○ ≤25% (limited to the base)
   ○ >25% and ≤50%
   ○ >50% and ≤75%
   ○ >75%
   ○ Inconclusive for HALT: imaging with insufficient image quality or presence of artifact
RLM
• Reduced leaflet excursion in the presence of HALT identified on computed tomography (2D multiplanar reconstructions or 3D volume rendering) and/or transesophageal echocardiography[b]
• The extent of RLM should be described per leaflet, using a 4-tier grading scale
   ○ None: no reduction in leaflet excursion
   ○ < 50% reduction in leaflet excursion
   ○ ≥ 50% reduction in leaflet excursion
   ○ Immobile: immobile leaflet
   ○ Inconclusive for RLM: imaging with insufficient image quality or presence of artifact

Severity
• Major: occludes part of the blood flow path, interferes with valve function (eg, immobility of 1 or more leaflets resulting in increased transvalvular gradient or reduced valve area), is symptomatic, or is sufficiently large to warrant treatment
• Minor: Absent or mild hemodynamic changes and absent symptoms or sequela compatible with valve thrombosis or thromboembolism (eg, subclinical)

Device erosion

Endocarditis

Frame fracture (replacement devices)
• Major: a break, tear, perforation, or other structural defect in the device (stent, housing, or leaflet) that results in either device failure, recurrent symptoms, or requires reintervention
• Minor: a break, tear, perforation, or other structural defect in the device (stent, housing, or leaflet,) not resulting in device failure, recurrent symptoms, or reintervention

Other device-specific endpoints

Number of devices used by intent to achieve the desired reduction in tricuspid regurgitation

Need for unplanned use of additional devices (eg, valves, clips, bands) as a result of failed implant delivery, detachment, fracture, or other failure

Inability to rerepair (defined as inability to maintain functional native tissue without prosthetic replacement performed via transcatheter or surgical means)

HALT = hypo-attenuated leaflet thickening; RLM = reduced leaflet motion.
[a]Computed tomography (CT) with high spatial and temporal resolution is required to accurately assess leaflet thickness and motion and a > 64 detector scanner is recommended. Typical CT acquisition parameters include: intravenous contrast-enhancement, submillimeter slice thickness, ECG gating with full cardiac cycle coverage and without dose modulation, target heart rate ≤70 beats/min. If CT is of either low quality, contraindicated, or inconclusive, transesophageal echocardiography may be used for the evaluation of leaflet thickness and motion.
[b]Additional leaflet assessments may include the following: 1) systolic measurements of maximal affected leaflet thickness and area on longitudinal and axial projections of the tricuspid valve, respectively; and 2) affected prosthetic leaflet(s) should be identified relative to the positions of the native commissures. Additional stent/frame assessments includes the following: 1) implant depth; 2) stent expansion and eccentricity at multiple levels; and 3) stent strut-separation at the annular level.

Table 20   Success Endpoints (Formerly Technical, Device, and Procedural Success)

I. Intraprocedural success

All of the following must be present:
(1)   Absence of intraprocedural mortality or stroke; and
(2)   Successful access, delivery, and retrieval of the device delivery system; and
(3)   Successful deployment and correct positioning of the intended device(s) without requiring implantation of unplanned additional devices; and
(4)   Adequate performance of the transcatheter device. Performance of devices whose purpose is a reduction in TR, should include the absence of tricuspid stenosis (TVA $\geq$ 1.5 cm^2 or TVAi $\geq$ 0.9 cm^2/m^2 [$\geq$ 0.75 if BMI > 30 kg/m^2], DVI < 2.2, mean gradient < 5 mm Hg); reduction of total tricuspid regurgitation to optimal ($\leq$ mild [1+]) or acceptable ($\leq$ moderate [2+]).
(5)   Absence of device-related obstruction of forward flow
(6)   Absence of device-related pulmonary embolism
(7)   Freedom from emergency surgery or reintervention during the first 24 h related to the device or access procedure.

II. Clinical success (assessed at 30 d and 1 y)

All of the following must be present at 30 d:
(1)   Absence of procedural mortality or stroke; and
(2)   Proper position of the device with adequate performance of the transcatheter device. Performance of devices whose purpose is a reduction in TR should include the absence of tricuspid stenosis (TVA $\geq$ 1.5 cm^2 or TVAi $\geq$ 0.9 cm^2/m^2 [$\geq$ 0.75 if BMI > 30 kg/m^2], DVI < 2.2, mean gradient < 5 mm Hg); reduction of total tricuspid regurgitation to optimal ($\leq$ mild [1+]) or acceptable ($\leq$ moderate [2+]); and
(3)   Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and
(4)   Absence of major device or procedure related serious adverse events, including:
    (a)   Life-threatening bleeding (TVARC 5)
    (b)   Major vascular complications
    (c)   Major cardiac structural complications
    (d)   Stage 2 or 3 acute kidney injury (includes new dialysis)
    (e)   Myocardial infarction or coronary ischemia requiring percutaneous coronary intervention or coronary artery bypass graft
    (f)   Device-related obstruction of forward flow
    (g)   Device-related pulmonary embolism
    (h)   Any severe hemodynamic compromise leading to heart transplantation or major cardiac assistance or patient extracorporeal membrane oxygenation dependent on day 30
    (i)   Any valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention

The following must be present at 1 y:
(5)   No rehospitalizations or reinterventions for the underlying condition (eg, tricuspid regurgitation/stenosis, heart failure); and
(6)   Improvement from baseline in symptoms (eg, NYHA improvement by $\geq$ 1 functional class); and/or Improvement from baseline in functional status (eg, 6-min walk test improvement by $\geq$ 50 m); and/or Improvement from baseline in quality-of-life (eg, Kansas City Cardiomyopathy Questionnaire improvement by $\geq$ 5)

BMI = body mass index; DVI = Doppler velocity index; NYHA = New York Heart Association; TR = tricuspid regurgitation; TVA = tricuspid valve area; TVAi = tricuspid valve area index; TVARC = Tricuspid Valve Academic Research Consortium.

complications, need for reintervention, or readmissions for the underlying condition (Table 20). Clinical success (measured at 30 days and beyond) incorporates ongoing valve performance as well as major adverse events, clinical outcomes, functional status, and quality-of-life metrics. This simplification of success endpoints, compared with more complex MVARC criteria in mitral therapies, will ease their implementation and interpretation in future clinical trials in TTVI.

Conclusions

Interest in pathophysiology, etiology, management, and outcomes of patients with TR has grown as a consequence of natural history studies showing progressively worse outcomes independently associated with increasing TR severity. This first TVARC document proposes standardized definitions of disease etiology and severity, as well as endpoints for trials that aim to address the gaps in our knowledge related to identification and management of patients with TR (Central Illustration). Standardizing endpoints for trials should provide consistency and enable meaningful comparisons between clinical trials. A second

TVARC document will focus on further defining trial endpoints and discuss trial design options.

Current State of Knowledge	Knowledge Gaps
TR etiologies may be associated with disparate outcomes	Can new classification and definitions of disease etiology help stratify patient outcomes?
There is a continuous risk of mortality associated with increasing severity of TR	Can an extended TR severity grading scale help stratify patient outcomes?
Guidelines have no Class I level of recommendations for medical management of TR	Can we define optimal medical therapy for TR patients?
Guidelines recommendations for surgical management of TR have poor penetration into clinical practice	Can risk for adverse outcomes be defined for different management strategies?
Transcatheter alternatives to surgical intervention are being investigated	Can we determine patient selection, goals of therapy, and clinically meaningful outcomes for transcatheter device therapies?

Central Illustration TVARC Definitions for Tricuspid Regurgitation Disease State and Trial Endpoints

Using consensus definitions of disease etiology and severity and adopting well-defined endpoints for trial design may reduce the knowledge gaps in our understanding of tricuspid regurgitation (TR). TVARC = Tricuspid Valve Academic Research Consortium.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Appendix

For a complete list of the TVARC Steering Committee as well as supplemental tables, please see the online version of this paper.

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