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Transcatheter treatment for tricuspid valve disease

Fabien Praz[1]*, MD; Denisa Muraru[2], MD; Felix Kreidel[3], MD; Philipp Lurz[4], MD; Rebecca T. Hahn[5], MD; Victoria Delgado[6], MD; Michele Senni[7], MD; Ralph Stephan von Bardeleben[3], MD; Georg Nickenig[8], MD; Jörg Hausleiter[9], MD; Antonio Mangieri[10], MD; Jose L. Zamorano[11], MD; Bernard Prendergast[12], MD; Francesco Maisano[13], MD

1. Bern University Hospital, University of Bern, Bern, Switzerland; 2. Department of Medicine and Surgery, University of Milano-Bicocca, Milan, and Istituto Auxologico Italiano, IRCCS, Department of Cardiological, Neural and Metabolic Sciences, San Luca Hospital, Milan, Italy; 3. Department of Cardiology, Heart Valve Center, University Medical Center Mainz, Mainz, Germany; 4. Department of Cardiology, Heart Center Leipzig at University of Leipzig, Leipzig, Germany; 5. Cardiology Department, NewYork-Presbyterian/Columbia University Medical Center, New York, NY, USA; 6. Department of Cardiology, Heart Lung Centre, Leiden University Medical Center, Leiden, the Netherlands; 7. Cardiology Division, Cardiovascular Department, Hospital Papa Giovanni XXIII, Bergamo, Italy; 8. Department of Internal Medicine II, Heart Center Bonn, University Hospital Bonn, Bonn, Germany; 9. Department of Cardiology, University Hospital, Ludwig-Maximilians-Universität München (LMU Munich), Munich, Germany; 10. Interventional Cardiology Unit, Maria Cecilia Hospital, GVM Care and Research, Cotignola, Italy; 11. Cardiology Department, University Hospital Ramón y Cajal, Madrid, and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; 12. Department of Cardiology, St Thomas' Hospital and Cleveland Clinic, London, United Kingdom; 13. Department of Cardiothoracic Surgery, IRCCS Ospedale San Raffaele, Milan, Italy

A list of collaborators can be found in the Appendix paragraph.

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KEYWORDS

- chronic heart failure
- imaging modalities
- transcatheter tricuspid valve intervention
- transoesophageal echocardiogram
- tricuspid valve disease
- tricuspid regurgitation

Abstract

Approximately 4% of subjects aged 75 years or more have clinically relevant tricuspid regurgitation (TR). Primary TR results from anatomical abnormality of the tricuspid valve apparatus and is observed in only 8-10% of the patients with tricuspid valve disease. Secondary TR is more common and arises as a result of annular dilation caused by right ventricular enlargement and dysfunction as a consequence of pulmonary hypertension, often caused by left-sided heart disease or atrial fibrillation. Irrespective of its aetiology, TR leads to volume overload and increased wall stress, both of which negatively contribute to detrimental remodelling and worsening TR. This vicious circle translates into impaired survival and increased heart failure symptoms in patients with and without reduced left ventricular ejection fraction. Interventions to correct TR are underutilised in daily clinical practice owing to increased surgical risk and late patient presentation. The recently introduced transcatheter tricuspid valve interventions aim to address this unmet need. Dedicated expertise and an interdisciplinary Heart Team evaluation are essential to integrate these new techniques successfully and select patients. The present article proposes a standardised approach to evaluate patients with TR who may be candidates for transcatheter interventions. In addition, a state-of-the-art review of the available transcatheter therapies, the main criteria for patient and device selection, and information concerning the remaining uncertainties are provided.

**Corresponding author: Department of Cardiology, Inselspital, University of Bern, Freiburgstrasse 15, CH-3010 Bern, Switzerland. E-mail: fabien.praz@insel.ch*

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Abbreviations

2D	two-dimensional
3D	three-dimensional
AF	atrial fibrillation
CCT	cardiac computed tomography
CIED	cardiac implantable electronic device
CMR	cardiac magnetic resonance
EROA	effective regurgitant orifice area
HF	heart failure
NOAC	non-vitamin K antagonist oral anticoagulants
PHT	pulmonary hypertension
SPAP	systolic pulmonary artery pressure
STR	secondary tricuspid regurgitation
TAPSE	tricuspid annular plane systolic excursion
TEE	transoesophageal echocardiography
TR	tricuspid regurgitation
TTE	transthoracic echocardiography
T-TEER	tricuspid transcatheter edge-to-edge repair
TTVI	transcatheter tricuspid valve intervention
TTVR	transcatheter tricuspid valve replacement
TV	tricuspid valve

Introduction

Tricuspid regurgitation (TR) is a common echocardiographic finding that is present in 70-90% of the general population[1]. While a trivial form is often seen in healthy individuals, moderate or severe TR has an age- and sex-adjusted prevalence of 0.55%, with a higher incidence in women and a strong age dependency[2] - approximately 4% of subjects aged 75 years or more have clinically relevant TR[2].

The development and successful results of transcatheter aortic valve implantation, followed by transcatheter therapies for mitral valve disease have opened a myriad of opportunities for transcatheter treatment of TR, a valvular heart disease that has traditionally been considered benign and often left untreated.

Chronic severe TR leads to volume overload and increased wall stress of the right ventricle (RV), which negatively contribute to detrimental remodelling and worsening TR. This vicious circle translates into impaired survival and increased heart failure (HF) symptoms in patients with and without reduced left ventricular ejection fraction[3-5]. Therefore, there is an unmet clinical need that requires prompt action. However, there remain many uncertainties and inconsistencies such as a non-systematic approach to assessing tricuspid valve (TV) disease, confusing terminology on anatomy and aetiology, as well as challenges in determining the mechanism and severity of TR and its consequences on the right chambers.

The present article proposes a standardised approach to evaluate patients with TR who may be candidates for transcatheter interventions. In addition, a state-of-the-art review of the available transcatheter therapies, the main criteria for patient and device selection, and information concerning the remaining uncertainties are provided.

ANATOMY OF THE TRICUSPID VALVE

The TV is the largest and most anterior cardiac valve with complex and variable anatomy[6]. Although its name infers the presence of three well-defined leaflets, numerous anatomical variations exist[7,8]. Differing terminology has been used[6-8] and a simplified nomenclature is proposed **(Figure 1)**[9] that has been derived from the analysis of 579 patients with various TR severity from 4 centres experienced in the assessement and treatment of TV disease. Based on the images provided, TV morphology could be determined in all but 4 patients (99%): 54% had type I, 4.5% had type II, 2.6% had type IIIA, 32.1% had type IIIB, 3.8% had type IIIC, and 2.4% had type IV. An in-depth understanding of the TV anatomy, in particular the number and location of supernumerary leaflets or scallops, is essential for procedural planning and may influence intervention outcome[10].

Transoesophageal echocardiographic (TEE) imaging from the transgastric short-axis view (or three-dimensional [3D] volume-

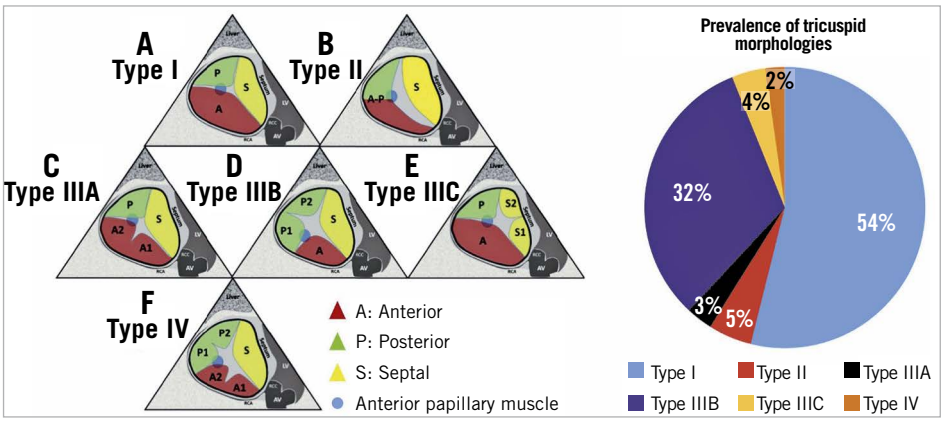


Figure 1. *Proposed nomenclature for tricuspid valve classification. Left panel. Proposed nomenclature for tricuspid valve classification scheme (anterior papillary muscle [blue circle] defines separation of anterior and posterior leaflets). A) Type I: 3-leaflet configuration. B) Type II: 2-leaflet configuration. C) – E) Type III: 4-leaflet configurations. F) Type IV: 5-leaflet configuration. Right panel. Incidence of each morphology. A: anterior leaflet; AV: aortic valve; P: posterior leaflet; S: septal leaflet. Adapted from Hahn et al[9], with permission.*

rendered equivalent) enables delineation of TV morphology. Steps to identify the leaflets are illustrated in **Supplementary Figure 1**.

CLASSIFICATION OF TRICUSPID REGURGITATION

Characterisation of the main morphologic and/or functional abnormalities resulting in TR is an essential aspect of transcatheter TV device selection. Primary TR results from anatomical abnormality of the TV apparatus and is observed in only 8-10% of patients with TV disease. Secondary TR (STR) is more common and arises as a result of annular dilation caused by RV enlargement and dysfunction due to pressure/volume overload as a consequence of pulmonary hypertension (PHT), often caused by left-sided heart disease, or atrial fibrillation (AF) with normal RV pressures (atrial/atriogenic or isolated TR). STR may also develop after left-sided valve surgery, probably due to silent ischaemic RV damage[11,12]. Implantation of cardiac implantable electronic device (CIED) RV leads provokes relevant TR in 20-30% of patients[13-15], which frequently progresses over time[16].

Carpentier's functional classification of leaflet mobility was intended to guide mitral valve surgical repair or replacement and its application to the TV is less well established[17]. In addition to differences in TV leaflet mobility, patients with STR also demonstrate variable remodelling of the TV annulus, right atrium (RA) and RV secondary to the underlying pathology[18]. Definition of different TR groups is prognostically important since disease aetiology determines long-term outcomes. Accordingly, we propose a novel integrative classification of TR **(Table 1)** that accounts for the pathophysiology, imaging characteristics, clinical management and outcome, while recognising that differentiation of the initial aetiology based on valve and chamber morphology/function may be challenging as TV disease progresses.

Table 1. Proposed new integrated classification of TR.

	Leaflet structure	Pathophysiology	Aetiology	Imaging
Secondary (functional)				
A. Atrial	Normal	RA enlargement and dysfunction leading to significant isolated annular dilation; RV often normal*	Carpentier I: Atrial fibrillation/flutter[101] Age[102] Heart failure with preserved ejection fraction[103,104]	Marked **TV annular dilation** is the dominant mechanism TV leaflet tethering is absent or minimal (except for late stages with secondary RV dysfunction) TV leaflet mobility is typically normal (Carpentier type I) RA is significantly dilated RV volume is typically normal (except in late stages)
B. Ventricular	Normal	RV enlargement and/or dysfunction leading to significant leaflet tethering and annular dilation	Carpentier IIIB: Left-sided ventricular or valve disease[11,12] Pulmonary hypertension[102] RV cardiomyopathy RV infarction	Marked **TV leaflet tethering** is the dominant mechanism TV leaflet mobility is typically restricted in systole (Carpentier type IIIB) TV annulus, RV and RA are dilated and/or dysfunctional
CIED-related	Normal/ abnormal	Leaflet impingement Leaflet/chordal entanglement/ chordal rupture Leaflet adherence Leaflet laceration/perforation Leaflet avulsion (following lead extraction)	Pacemaker Implantable cardiac defibrillator (ICD) Cardiac resynchronisation therapy (CRT) devices[105-108]	**TV leaflet structural abnormalities** may be present TV leaflet mobility is variable (all Carpentier types) TV annulus, RV and RA are typically dilated (except for acute TR)
Primary (organic)	Abnormal	Lack of leaflet coaptation due to intrinsic changes leading to restricted or excessive leaflet mobility or leaflet perforation	Carpentier I: Congenital Endocarditis Carpentier II: Myxomatous disease Traumatic Post biopsy Carpentier IIIA: Carcinoid[109] Rheumatic Radiotherapy Tumours	**TV leaflet structural abnormalities** characteristic of each primary aetiology are the dominant mechanisms TV leaflet mobility is variable (all Carpentier types) TV annulus, RV and RA are typically dilated (except in acute TR)

*RV basal diameter may appear abnormal due to the conical RV shape. CIED: cardiac implantable electronic device; CRT: cardiac resynchronisation therapy; ICD: implantable cardiac defibrillator; RA: right atrium; RV: right ventricle; TR: tricuspid regurgitation; TV: tricuspid valve

DEFINITION OF DISEASE SEVERITY

The functional anatomy of the TV apparatus can be evaluated by 3D transthoracic echocardiography (3D-TTE) and/or 3D-TEE, and severity of TR assessed using semi-quantative parameters of colour and spectral Doppler **(Supplementary Figure 2)**[19]. Additional advanced imaging may be of value when echocardiography is either of insufficient quality or inconclusive **(Table 2)**. Specific signs of severe TR include wide systolic leaflet separation, hepatic vein systolic flow reversal demonstrated by pulsed-wave Doppler, and a triangular (early peaking) continuous-wave Doppler TR signal. RV and RA dilatation are supportive signs. The TR colour jet is not a measure of regurgitant volume, but is determined by jet momentum. Thus, whilst a small colour TR jet may reliably reflect trivial or mild TR and a very large jet is specific to severe TR, patients with PHT may demonstrate larger jets that overestimate TR orifice area. Furthermore, rapid equalisation of RA and RV pressures in severe TR may be associated with non-aliasing jets.

Quantitative measures of TR are therefore essential to define severity, including estimation of anatomical regurgitant orifice area by vena contracta measurement and quantification of physiological effective regurgitant orifice area (EROA) and regurgitant volume (RVol). A vena contracta ≥7 mm generally indicates severe TR[19,20], although some studies suggest a threshold of 9 mm averaged from two orthogonal 2D views[21]. The TR coaptation zone is frequently non-circular and measures of vena contracta width relying on single 2D imaging may be inaccurate – planimetry using 3D colour assessment may therefore be conceptually more appropriate.

Accumulating evidence links EROA to outcome in various settings[22,23] and current American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines define severe TR as an EROA ≥0.40 cm^2 and RVol ≥45 mL[20,24]. However, since patients undergoing transcatheter TV interventions (TTVI) frequently have an anatomical regurgitant area several times greater than an EROA of 0.40 cm^2, an extended classification to include "massive" and "torrential" TR (both associated with detrimental outcomes) has recently been proposed **(Supplementary Table 1)**[23-27]. Studies using cardiac magnetic resonance (CMR) quantitation suggest that patients with a TR regurgitant volume ≥45 ml or regurgitant fraction ≥50% have the highest risk of excess mortality[28] **(Table 2)**.

ASSESSMENT OF RV SIZE AND FUNCTION

Comprehensive RV assessment in patients with severe TR should be performed in a euvolemic state and include standard echocardiographic measures of RV size and function, and quantification of RV morphological, functional, and tissue remodelling **(Figure 2, Table 2)**. Standard echocardiographic measures of RV size and function are listed in **Supplementary Table 2**[29]. Assessment of RV strain using 2D echocardiography or CMR is less load dependent than tricuspid annular plane systolic excursion (TAPSE) in severe TR and more sensitive in the detection of early RV dysfunction and prediction of overall clinical outcome[30]. RV ejection

Table 2. Imaging modalities for diagnosis of tricuspid valve disease and guidance of transcatheter tricuspid valve interventions.

Imaging modality	Applications
TTE	Grading of TR severity
	Assessment of TV pathology and mechanism(s) of TR
	Diagnosis/classification of PHT
	Evaluation of RV function
	Determination of pacemaker/defibrillator lead location and evaluation of TV leaflet lead impingement
TEE (3D)	Assessment of TV pathology and mechanism(s) of TR
	Exclusion of intracardiac thrombus/masses
	Determination of pacemaker/defibrillator lead location and evaluation of TV leaflet lead impingement
	Evaluation of TEE imaging quality in supine position
	Procedural guidance
ICE (3D)	Procedural guidance in patients with insufficient TEE quality or contraindications to oesophageal intubation
	Avoidance of extracardiac or left heart artefacts
	Elimination of the need for systematic general anaesthesia
CCT	Assessment of annular shape, dimensions and annular calcification
	Determination of the location of pacemaker/defibrillator leads
	Definition of optimal procedural fluoroscopic angulations
	Assessment of the relationships of the tricuspid annulus to surrounding structures (particularly the RCA)
	Evaluation of specific annular anchor points in relation to tricuspid leaflet hinge points and coronary arteries
	Evaluation of RCA status
	Evaluation of the relationship between IVC and TV annulus
Coronary angiography/ fluoroscopy	Evaluation of RCA status
	Navigation and control of patency of the RCA if a device is anchored to the tricuspid annulus
	Orientation and device placement/deployment (in particular in case of multiple implants)
CMR	Grading of TR severity when echocardiographic quantification is inconclusive
	Evaluation of RV function
	Assessment of myocardial fibrosis

CCT: cardiac computed tomography; CMR: cardiac magnetic resonance; ICE: intracardiac echocardiography; IVC: inferior vena cava; PHT: pulmonary hypertension; RCA: right coronary artery; RV: right ventricle; TEE: transoesophageal echocardiography; TR: tricuspid regurgitation; TTE: transthoracic echocardiography; TV: tricuspid valve

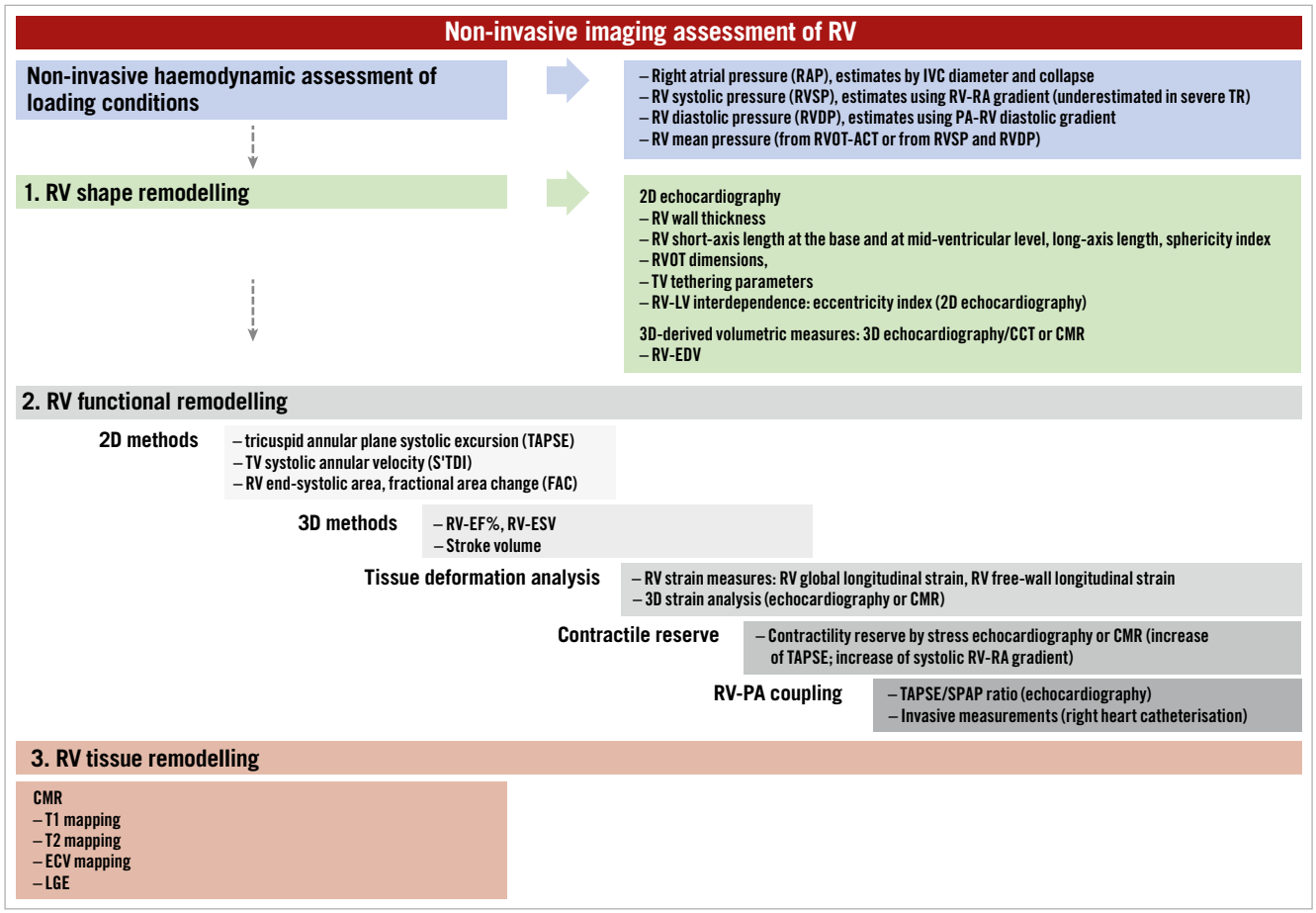


Figure 2. *Imaging assessment of the right ventricle. 2D: two-dimensional; 3D: three-dimensional; ACT: acceleration time; CCT: cardiac computed tomography; CMR: cardiac magnetic resonance; ECV: extracellular volume; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; IVC: inferior vena cava; LGE: late gadolinium enhancement; LV: left ventricle; PA: pulmonary artery; RV: right ventricle; RVOT: right ventricular outflow tract; SPAP: systolic pulmonary artery pressure; TV: tricuspid valve*

fraction can be measured using various imaging modalities (CMR, 3D echocardiography, cardiac computed tomography [CCT]) but it fails to account for the relationship between RV contractility and afterload, and may therefore overestimate RV systolic function in severe TR. The TAPSE/systolic pulmonary artery pressure (SPAP) ratio, a non-invasive marker of RV-pulmonary arterial coupling, may overcome this limitation and its prognostic value has been demonstrated under several conditions[31,32], including severe TR where a TAPSE/SPAP ratio <0.31 mm/mmHg indicates poor prognosis[33]. In a recent propensity matched analysis, patients with mid-range RV dysfunction (TAPSE 13-17 mm) appeared to derive the greatest benefit from TTVI[34].

The demonstration of contractile reserve in response to pharmacological or physical stress has prognostic relevance in patients with pulmonary hypertension and severe baseline RV dysfunction[35-37]; further studies are needed to explore the role of stress imaging in severe TR.

Right heart catheterisation is the gold standard for the assessment of the severity and mechanism of PHT, pulmonary vascular resistance, RA pressure/pulmonary capillary wedge pressure ratio, pulmonary artery pulsatility index, and the reversibility of PHT[38,39]. Moreover, an impaired afterload-corrected TAPSE to invasive SPAP obtained during right heart catheterisation and a discordant diagnosis of PHT (>10 mmHg difference between non-invasive and invasive SPAP) were independent predictors of worse outcomes (death, HF hospitalisation, and re-intervention) in patients with severe TR[40].

Finally, detection of myocardial fibrosis by CMR[41-43] has prognostic importance in RV failure and may help to define the optimal timing of intervention in severe TR.

PATIENT MANAGEMENT AND SELECTION

STR is associated with a variety of medical conditions and may present to a range of specialists (i.e., not only cardiologists). Efforts should be made to increase the clinical awareness of its consequences and emerging treatment options. All risk groups (those with left-sided heart disease, AF, previous mitral valve surgery, pre-capillary PHT, CIED RV lead) with symptoms/signs of congestive HF (jugular vein congestion, dyspnoea, peripheral oedema, renal failure, liver and gut congestion) should be

specifically evaluated for the presence of significant STR. Initial consultation and echocardiography to confirm the diagnosis and assess TR severity and RV function should be followed by early referral to a centre with expertise in the treatment of TV disease where work-up may be completed by right and left heart catheterisation and advanced imaging studies **(Table 2)**.

Currently, more than 90% of the patients with clinically relevant TR are not offered any treatment[44], mainly due to the long-standing misconception that STR improves after treatment of left-sided heart disease, despite the fact that STR progresses in up to 25% of patients after open heart surgery[11,12]. Furthermore, relatively high mortality rates (8.8%-9.7%) have been reported after conventional surgery for isolated TR, usually as a result of late referral[45-48]. However, according to single-centre studies including younger and less sick patients compared to the TTVI cohorts, tricuspid surgery may be safe and effective when performed in experienced centres[49,50].

Regardless of symptomatic status and clinical presentation, patients with severe STR should first be treated for the assumed underlying condition (e.g., restore sinus rhythm in patients with AF if feasible, optimise medical treatment of HF or PHT) followed by re-evaluation using the same imaging modality (ideally at the same imaging laboratory) **(Figure 3, Supplementary Table 3)**. Repositioning or extraction of CIED RV leads can be envisaged in selected patients with disturbed TV leaflet motion. However, the efficacy of this procedure in reducing TR is uncertain and additional damage to the TV valve can occur[51].

The indication for any TV intervention and its timing should take account of multiple factors, including the patient's clinical characteristics, disease severity, concomitant end-organ function and anatomical considerations **(Figure 4)**. Those who remain symptomatic and fluid overloaded despite diuretic treatment with mild or moderate left ventricular impairment, preserved RV function, no evidence of pre-capillary PHT, and only mild/moderate renal and liver dysfunction may derive the greatest benefit from TV intervention (**Figure 4**, central column). Combined procedures may be considered in patients with associated mitral or aortic valve disease[52] – a staged approach is often appropriate since TR and RV dimensions improve in about 40% of patients within three months of successful transcatheter treatment of mitral regurgitation[53]. Conversely, the procedure may be futile in candidates with end-stage HF, untreated pre- and post-capillary PHT or severe pulmonary fibrosis. Even if evidence is missing at this stage, advanced end-organ damage, i.e., terminal renal failure or manifest liver cirrhosis, need to be taken into account, in particular if the estimated life expectancy is less than one year (**Figure 4**, right column).

Patients presenting with refractory hypervolemic state before the procedure may benefit from in-patient medical treatment optimisation, in particular a course of intravenous diuretics. This may favourably modify right chamber anatomy, annulus size, and reduce large coaptation gaps, therefore facilitating interventional treatment.

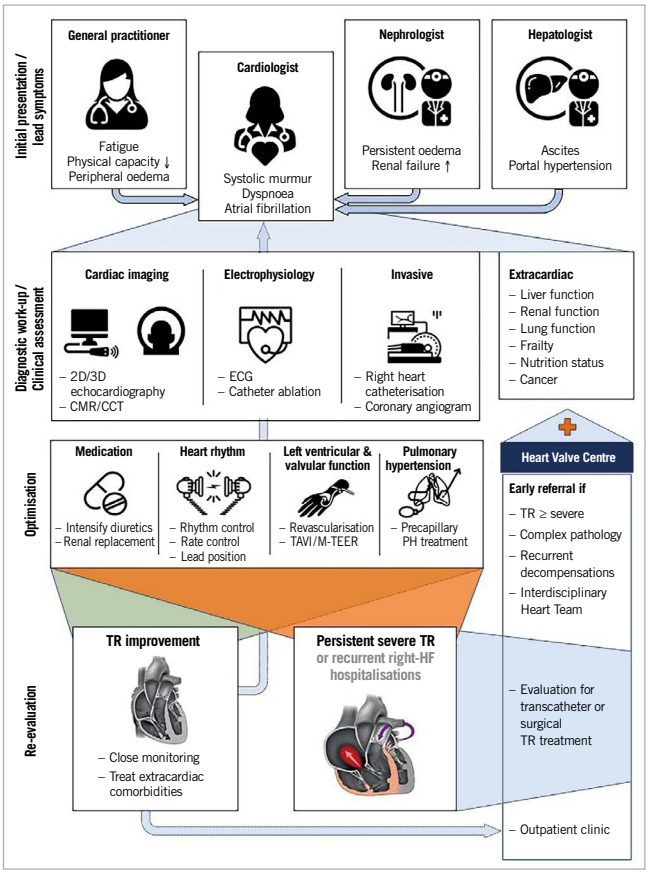


Figure 3. *Care pathways for patients with severe tricuspid regurgitation. 2D: two-dimensional; 3D: three-dimensional; CCT: cardiac computed tomography; CMR: cardiac magnetic resonance; ECG: electrocardiogram; HF: heart failure; M-TEER: mitral transcatheter edge-to-edge reapair; PH: pulmonary hypertension; TAVI: transcatheter aortic valve implantation; TR: tricuspid regurgitation*

TRANSCATHETER TREATMENT OPTIONS AND DEVICE SELECTION

Current transcatheter treatment options mimic surgical techniques and include approved solutions in Europe, such as leaflet approximation, direct annuloplasty and heterotopic caval valve implantation, as well as not yet commercially available transcatheter TV replacement (TTVR) systems using orthotopic valve implantation **(Figure 5)**. Growing evidence supports the use of TTVI in inoperable or surgical high-risk patients: mortality was lower following intervention using various devices compared to standard medical treatment in two propensity score-matched cohorts[34,54], accompanied by reduction in the rate of HF re-hospitalisation (26±3% vs 47±3% p<0.0001) at one-year follow-up[54]. Confirmation of these findings in randomised controlled trials is needed.

Based on the aforementioned evidence, the 2021 Valvular Heart Disease guidelines of the European Society of Cardiology first give a IIb level C recommendation for transcatheter treatment of severe symptomatic TR in inoperable patients, while the importance of early referral of patients with TV disease, as well as the

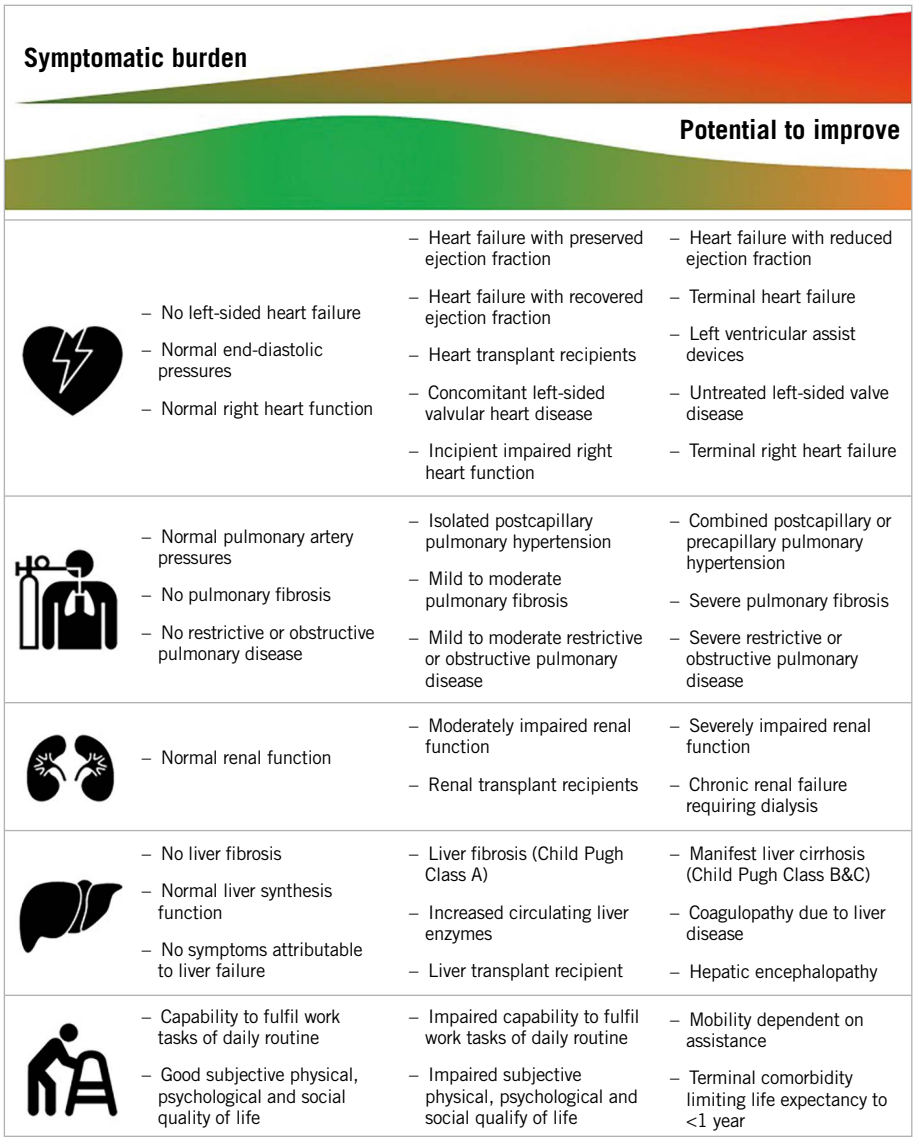


Figure 4. *Clinical, anatomical and physiological factors suggesting a positive symptomatic response to tricuspid valve treatment.*

role of concomitant treatment of the TV during left-sided heart surgery, are reinforced[55].

Compared to mitral procedures, TTVI presents several additional technical and anatomical challenges, including difficult visualisation of the TV apparatus, variable anatomy with thinner valve leaflets, and a large coaptation gap. Proposed criteria and an algorithm used for device selection are shown in **Table 3** and **Figure 6**.

LEAFLET APPROXIMATION

Tricuspid transcatheter edge-to-edge repair (T-TEER) using the TriClip™ (Abbott Vascular, Santa Clara, CA, USA) or leaflet approximation with the PASCAL systems (Edwards Lifesciences, Irvine, CA, USA) are approved in Europe for minimally invasive TV repair. These techniques are the most frequently used worldwide as a result of their safety, availability, and ease of use. Whilst initially performed "off-label" using the MitraClip® system (Abbott Vascular)[56-58], a dedicated T-TEER device with a shorter curve guiding catheter and additional steerable plane of motion (septal to lateral), the TriClip, has been developed to facilitate TV access. In the core lab-adjudicated TRILUMINATE study, T-TEER in 85 prospectively enrolled patients (STR 84%; severe, massive and torrential in 29%, 26% and 37%, respectively) was associated with a durable reduction to moderate TR or less in 71% at one year, accompanied by symptomatic improvement (83% of the patients were in New York Heart Association [NYHA] Class I or II at 12 months), and 40% reduction in the rate of re-hospitalisation[59,60]. In addition, improvement of the six-minute walking distance by 31±10.2 metres and Kansas City Cardiomyopathy Questionnaire by 20±2.61 points were observed, along with a significant reduction of the RV and RA dimensions and improvement

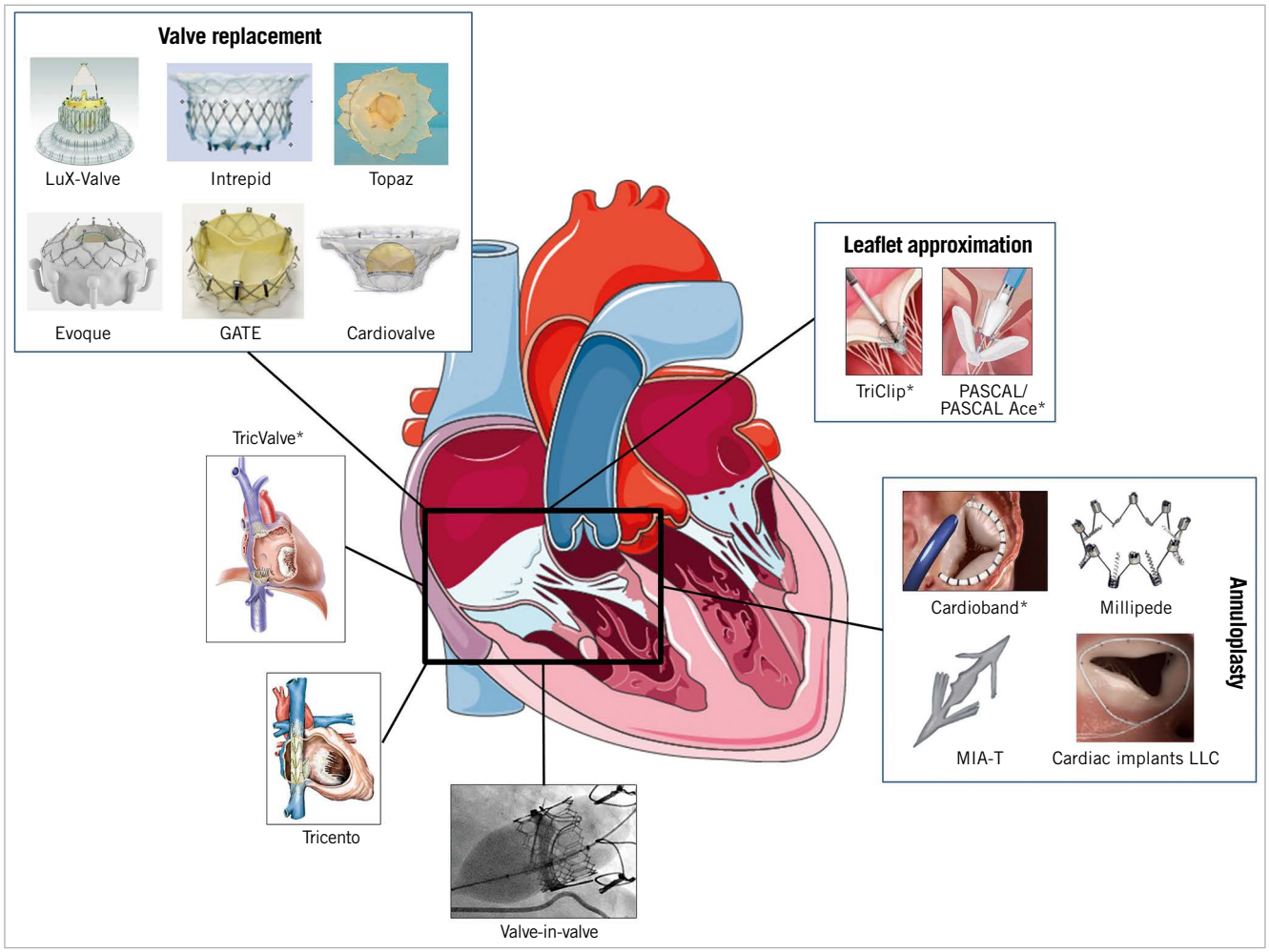


Figure 5. *Transcatheter tricuspid systems that are approved or under clinical evaluation. * with CE approval.*

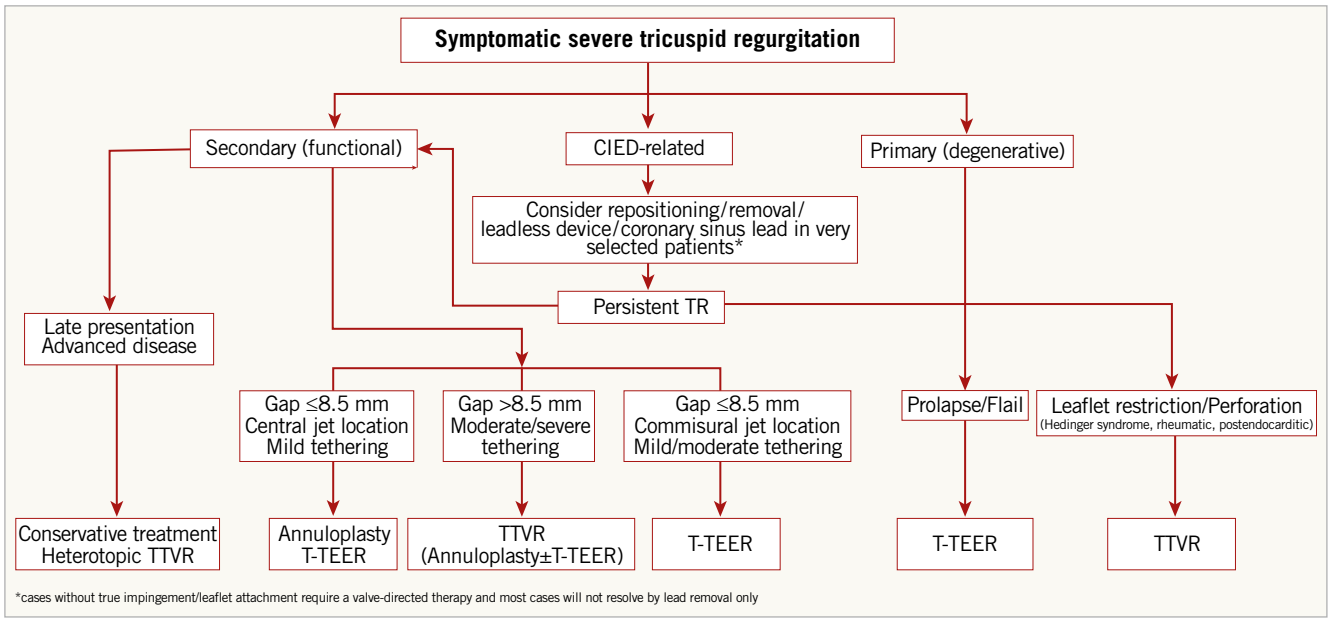


Figure 6. *Proposed algorithm for the selection of TTVI systems. CIED: cardiac implantable electronic device; T-TEER: tricuspid transcatheter edge-to-edge repair; TTVR: transcatheter tricuspid valve replacement*

Table 3. Anatomical criteria for device selection.

Strategy	Favourable anatomy	Feasible anatomy	Unfavourable anatomy
Leaflet approximation	Small septolateral gap ≤7 mm[10] Anteroseptal jet location Confined prolapse or flail Trileaflet morphology	Septolateral coaptation gap >7 but ≤8.5 mm[65] Posteroseptal jet location Non-trileaflet morphology Incidental CIED RV lead (i.e., without leaflet impingement)	Large septolateral coaptation gap >8.5 mm[65] Leaflet thickening/shortening (rheumatic, carcinoid)/perforation Dense chordae with marked leaflet tethering Anteroposterior jet location Poor echocardiographic leaflet visualisation CIED RV lead leaflet impingement Unfavourable device angle of approach
Annuloplasty	Annular dilatation as primary mechanism of TR Mild tethering (tenting height <0.76 cm, tenting area<1.63 cm^2, tenting volume [3D] <2.3 mL)[110,111] Central jet location Sufficient landing zone for anchoring	Moderate tethering (tethering height ≥0.76 cm but <1.0 cm, tenting area >1.63 but <2.5 cm^2, tenting volume [3D] ≥2.3 mL but ≤3.5 mL)[110,111] Incidental CIED RV lead (i.e., without leaflet impingement)	Excessive annular dilatation (exceeding device size) Severe tethering (tethering height >1.0 cm, tenting volume >3.5 mL). Poor echocardiographic annular visualisation[110,111] Annular proximity of RCA CIED RV lead leaflet impingement
Orthotopic valve implantation	Previous surgical repair or bioprosthetic valve replacement Leaflet thickening/shortening (rheumatic, carcinoid) Incidental CIED RV lead (i.e., without leaflet impingement) Any leaflet morphology	Large coaptation gap CIED RV lead leaflet impingement	Excessive annular dilatation (exceeding device size) Unfavourable device angle of approach Severe right ventricular dysfunction
Heterotopic valve implantation	Appropriate caval diameters (and intercaval distance) No option for direct valve treatment		Proximity of the RA to the orifice of the liver veins (<10-12 mm) Severely increased pulmonary artery and RA pressures due to the risk of fracture of bicaval valved stents

3D: three-dimensional; CIED: cardiac implantable electronic device; RA: right atrium; RCA: right coronary artery; RV: right ventricular; TR: tricuspid regurgitation

of the RV systolic function. Previous observational studies have demonstrated reverse RV remodelling[61], improved cardiac output[62], and reduction of liver enzymes in patients with documented congestion following T-TEER[63]. Early experience with the first version of the system identified an increased risk of single leaflet device attachement in comparison with mitral procedures (about 7% in the TRILUMINATE study). A large coaptation gap (>7-10 mm) and non-anteroseptal location of the TR jet have also been associated with procedural failure with the same version of the device[10,64]. Using the XTR implant with extended clip arms, a coaption gap ≤8.4 mm predicted successful reduction to moderate TR or less **(Table 3)**[65]. The latest TriClip Gen 4 iteration of the system offers four different implant sizes and controlled gripper actuation to permit optimised independent leaflet grasping.

Comparable results have been obtained with the PASCAL system in a compassionate use cohort[30], as well as in a US-based early feasibility study[66]. Although less experience has been accumulated so far, the number of procedures has grown rapidly since introduction of the smaller PASCAL Ace (Edwards Lifesciences) device that facilitates navigation of the TV anatomy. The novel DragonFly™ transcatheter mitral valve repair device (Valgen Medical, Hong Kong, China) has recently been used successfully for mitral intervention[67], and its use for TV repair is under current investigation.

ANNULOPLASTY

The Cardioband™ direct annuloplasty system (Edwards Lifesciences) obtained CE mark for the treatment of patients with severe symptomatic STR in 2018. In the European approval study (TRI-REPAIR), the device – consisting of a screw-anchored adjustable band – was successfully implanted in all 30 patients with sustained reduction of TR to moderate or less in 76% at 30 days, 73% at 6 months[68] and 72% at 2 years[69], and more than 80% of the patients in NYHA Class I/II throughout the follow-up period. Similarly, a 20% reduction in septolateral diameter was achieved in the post-market core laboratory adjudicated TriBAND study, translating into reduction of TR to moderate or less in 69% of patients at 30 days[70]. Of note, patients included in both studies had higher EROA at baseline compared to those in TRILUMINATE (TRI-REPAIR 0.79±0.51, TriBAND 0.76±0.48, TRILUMINATE 0.65±0.03), suggesting the inclusion of candidates with more advanced disease[71]. In another study including

60 patients of whom 51.7% had massive or torrential and 48.3% severe TR, 60.3% of patients had less-than-severe TR at discharge[72]. Particular care is required during deployment to avoid right coronary artery perforation or occlusion that occurred in 15% of the cases during the early experience (although transient deformation may not lead to clinical consequences)[72,73]. These results emphasise the need for further technical refinement along with careful patient selection and preprocedural planning.

Other annuloplasty techniques are under clinical investigations. The Millipede ring (Boston Scientific, Marlborough, MA, USA) has been implanted surgically in two patients[74] and a transcatheter approach is in development. The MIA™-T system (Micro Interventional Devices, Newtown, PA, USA), a sutureless transcatheter annuloplasty system, is being investigated in a study (STTAR study) using both the surgical and transcatheter approach. Furthermore, successful implantation of a two-stage percutaneous annuloplasty system (Cardiac Implant LLC, Tarrytown, NY, USA) was reported in 2020[75].

TRANSCATHETER TRICUSPID VALVE REPLACEMENT

TTVR was first performed in 2017 using the GATE™ bioprosthesis (NaviGate Cardiac Structures, Inc., Lake Forest, CA, USA) that was introduced mainly via the transatrial surgical route using a 42 Fr catheter delivering an up to 54 mm stented valve[76,77]. Technical success was achieved in 26/30 (87%) consecutive patients with relevant conduction disturbances in 10% and conversion to open heart surgery in 5%. In-hospital mortality was relatively high (10%) in this early experience and inotropic support was required in 57% of patients, most probably due to transient RV failure[78].

The LuX-Valve (Ningbo Jenscare Biotechnology Co. Ltd., Ningbo, China) is another 32 Fr system inserted via the transatrial access that can anchor to the septum and simultaneously grasp the anterior TV leaflet. Initial experience in 46 patients was associated with high technical success (97.8%) – one patient developed fatal RV perforation – and an in-hospital mortality rate of 13%[79].

Surgical thoracotomy is associated with significant morbidity in patients with advanced disease, encouraging a move towards transfemoral systems. The EVOQUE bioprosthesis (Edwards Lifesciences) is delivered using a 28 Fr catheter and is available in three sizes (44, 48, and 52 mm). The system has been investigated on a compassionate use basis in 25 patients with successful implantation in 92%, reduction of TR to mild or trace in 100%, and no deaths, coronary complications, or valve migration. A permanent pacemaker implantation was required in 8%, and 76% of patients were in NYHA Class I/II at 30 days[80]. Preliminary results of the single-arm early TRISCEND feasibility study have been equally encouraging with an all-cause mortality rate of 3.8% at one month [Kodali S. TRISCEND study 30-day outcomes after transfemoral tricuspid valve replacement. EuroPCR 2021].

Transfemoral implantation of the Intrepid™ (Medtronic, Minneapolis, MN, USA) available in 42 and 48 mm sizes, the Cardiovalve (Cardiovalve Ltd., Or Yehuda, Israel), and the Topaz (TRiCares, Aschheim, Munich, Germany) transfemoral systems have also been reported in individual patients. Another self-expanding unileaflet stented bioprosthesis, the Trisol valve (Trisol Medical, Yokneam, Israel), is introduced via the jugular access and has recently been successfully used in humans.

Off-label transcatheter valve-in-valve implantation of the SAPIEN 3 aortic bioprosthesis (Edwards Lifesciences) is a safe and effective treatment option in patients with a degenerating surgical tricuspid bioprosthesis[81], while suboptimal results have been observed after tricuspid valve-in-ring procedures[82,83].

HETEROTOPIC CAVAL VALVE IMPLANTATION

Heterotopic caval valve implantation can mitigate symptoms related to TR and associated RV failure without treating its cause and is therefore a useful symptomatic treatment option in patients who are unsuitable for other transcatheter or surgical procedures. Conventional aortic balloon-expandable bioprostheses are too small in this setting and associated with deleterious embolic complications[84]. This has led to the development of the dedicated TricValve® (P+F Products+Features GmbH, Wessling, Germany) and TRICENTO^{M2M} (MEDIRA GmbH, Balingen, Germany) devices. While TricValve features two valves implanted separately in the superior and inferior vena cava, TRICENTO^{M2M} consists of a custom-made single valved stent linking both venae cavae. In their current iteration, both devices can treat patients with diameters of the inferior vena cava (IVC) up to 40-43 mm, while the distance from the RA junction to the hepatic veins needs to be at least 10 mm. Successful implantations of both devices have been reported in individual patients[85-87], although recently described fractures of the TRICENTO^{M2M} stent frame in patients with massive or torrential TR have led to design modification and adjustement of clinical selection criteria. Further evaluation in larger cohorts is required to understand the role and implications of this therapy better.

INTERVENTIONAL IMAGING

3D-TEE is essential for intraprocedural guidance during TTVI and the mid- and deep-oesophageal (RV inflow/outflow) and transgastric windows are of particular value **(Figure 7)**. Beyond leaflet approximation, all other transcatheter techniques require dedicated preprocedural CCT assessement of the tricuspid annular and subvalvular anatomy, as well as RA and caval dimensions[88]. Implant simulation and real-time fusion of CCT, fluoroscopy and echocardiographic images may also assist in some procedures.

It is essential to understand that interventionalists and imaging specialists approach the TV apparatus from different perspectives. During intraprocedural imaging, the TEE probe is behind the heart, generating TV images in the "valentine" position **(Supplementary Figure 3A-Supplementary Figure 3C)**. However, movement of catheters during TTVI, spatial relationships of the TV with adjacent structures (particularly the IVC) and the direction of predominant annular dilation are better understood when labelling TV structures using the "attitudinal" nomenclature. CCT can also be used to demonstrate the anatomic relationships of the TV using a fluoroscopy-like display **(Supplementary Figure 3D-Supplementary Figure 3F)**.

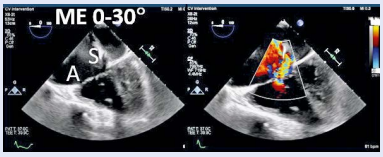
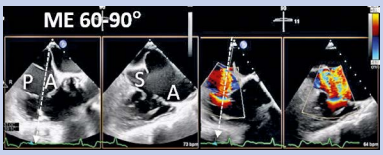
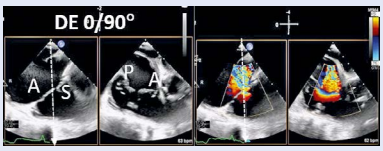
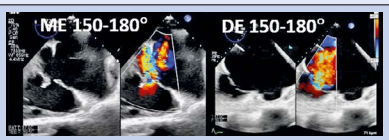
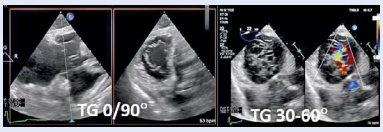
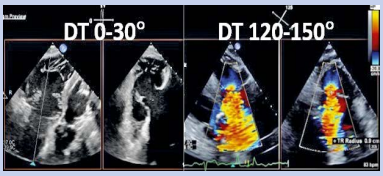
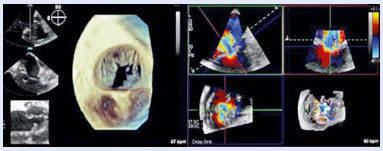
View	Imaging examples	Structures imaged	Potential role in procedural guidance
4-chamber view, ME (0-30°)		– Tricuspid valve (A, S) – Right atrium/right ventricle/ outflow – Left atrium/ventricle – Aortic valve	– Septal and anterior tricuspid valve leaflets (for TEER) and annulus (for annular or replacement devices).
RV inflow/outflow view, ME (60-90°)		– Tricuspid valve (A, P, S) – Right atrium/right ventricle	– Imaging sweep from anterior to posterior to localise regurgitant orifice along the septal coaptation line. – Biplane imaging used to visualise A-S or P-S coaptation zone or annulus.
2-chamber view, DE (0-30°) and RV inflow/outflow view, DE (60-90°)		– Tricuspid valve (A or P, S) – Right atrium/right ventricle – Coronary sinus	– Septal and anterior (or posterior, depending on depth/flexion) tricuspid valve leaflets (for TEER) and annulus (for annular or replacement devices).
Reversed 4-chamber view, ME and DE (150-180°)		– Tricuspid valve (A, S) – Right atrium/right ventricle – Coronary sinus	– Septal and anterior tricuspid valve leaflets (for TEER) and annulus (for annular or replacement devices).
2-chamber view, TG (30-60°) Short-axis view, TG (30-60°)		– Tricuspid valve SAX (A, S, P or atypical morphology) – Regurgitant orifice (SAX) – Right ventricular outflow	– Tricuspid coaptation gaps, regurgitant orifice location and chordal anatomy help guide TEER. – Posterior annulus well imaged for annular or replacement device.
Apical view, DT (0-30° or 120-150°)		– Tricuspid valve (A, S) – Right atrium/right ventricle/ outflow – Left ventricular outflow – Aortic valve	– Septal and anterior tricuspid valve leaflets (for TEER) and annulus (for annular or replacement devices). – TR Doppler aligned for quantitative analysis.
3D volumes (any level)		– Tricuspid valve SAX (A, S, P or atypical morphology) – Regurgitant orifice (SAX)	– 3D multiplanar reconstruction allows simultaneous imaging of coaptation gaps, regurgitant orifice location and leaflet lengths/mobility for device implantation.

Figure 7. *TEE views during transcatheter TV intervention. Deep oesophageal view for biplane imaging and acquisition of 3D volumes. The transgastric view is the only 2D view that allows simultaneous visualisation of all three TV leaflets. 3D: three-dimensional; A: anterior; DE: deep oesophageal; ME: mid-oesophageal; P: posterior; S: septal; TG: transgastric; RV: right ventricle; SAX: short axis; TEER: transcatheter edge-to-edge repair*

Clear and continuous communication and understanding between the interventional echocardiographist and TV interventionalist is key to procedural success. Speaking the same anatomical and directional language requires mutual knowledge of imaging, devices and the procedure, and can only be achieved by joint training of the TV transcatheter team. Standardisation of right chamber views using the "attitudinal" orientation and nomenclature (in which the displayed image and relationships of the TV leaflets with adjacent cardiac structures are identical irrespective of the imaging modality) provides the basis for a common language used by interventional and imaging specialists[89].

Use of intracardiac echocardiography (ICE) is helpful in patients with insufficient imaging quality[90-92] and will certainly increase once novel 4D catheters allowing 3D imaging and multiplanar reconstruction become broadly available[93]. This may reduce the need for general anesthesia in the future.

POST-PROCEDURAL MANAGEMENT

Since AF is highly prevalent in patients presenting with severe TR (about 70%), post-procedural anticoagulation with either warfarin/coumadin or non-vitamin K antagonist oral anticoagulants (NOAC) is usually required. Patients in sinus rhythm with no other

indication for anticoagulation should use the same antiplatelet regimen as after transcatheter mitral valve repair (usually four weeks of aspirin plus clopidogrel, followed by aspirin daily). The optimal antithrombotic regimen following TTVR is unclear, although early experience indicates that a warfarin-/coumadin-based anticoagulation regimen (possibly combined with aspirin for at least one year) might be preferred.

The preprocedural diuretic regimen should be maintained for at least three months after the procedure to allow RV reverse remodelling. However, careful dose reduction may be required in TTVR patients who develop early post-procedural polyuria (usually within 24-48 hours) as a result of improved cardiac output and reduced venous congestion, or in those who develop symptomatic hypotension and/or renal failure over longer-term follow-up. Given the need for frequent modification of the post-procedural diuretic and HF medication regimen, most sites recommend initial outpatient follow-up at 1, 6, and 12 months, followed by annual review. Assessment may include blood tests for NT-proBNP, renal and liver function, transthoracic echocardiography, a six-minute walk-test and a quality-of-life questionnaire.

Although systematic evidence is lacking, early experience suggests that glifozines (sodium glucose cotransporter 2 [SGLT-2] inhibitors) may be of particular benefit in selected patients with right-sided HF following TV intervention due to their diuretic, nephro-protective and symptomatic effects.

Periprocedural and early post-procedural antibiotic prophylaxis should be used in all patients undergoing TTVI to prevent infective endocarditis. After discharge, established endocarditis prophylaxis guidelines should be followed, although a lower threshold for treatment might be appropriate due to an increased probability of bacteraemia in the venous circulation.

PROPOSED REQUIREMENTS FOR A HEART VALVE CENTRE WITH EXPERTISE IN TRICUSPID VALVE TREATMENT

A multidisciplinary Heart Team approach is recommended for the evaluation of patients with TV disease in a Heart Valve Centre with expertise in a broad spectrum of diagnostic and therapeutic solutions **(Table 4)**[94]. Essential requirements include an interventional cardiology team with broad expertise in heart valve interventions, experience in advanced multimodality TV imaging (including high quality CCT and CMR for specific indications) and easy access to cardiac surgery counselling. A cardiac surgery department on site with operator experience in TV surgery, as well as an intermediate and intensive care unit (or alternatively a dedicated structural and valve unit) with collaborative links with other cardiac services (particularly an HF team) are mandatory, when investigational and replacement systems are used.

A Heart Valve Centre with expertise in TV treatment should build a referral and educational network with collaborating partners and offer easily accessible digital (imaging) data transfer solutions to enable remote consultation and case discussion. Finally, participation in multicentre studies assessing new treatment approaches for TR is of utmost importance given the need for greater understanding of the indications, timing and technical success of invasive TV treatments.

Table 4. Proposed requirements for a heart valve centre with expertise in TV interventions.

Minimal requirements	Additional optional requirements
Interventional cardiology	
Expertise in valvular heart intervention especially on the mitral and tricuspid valves	Experience in percutaneous extracorporeal life support
Cardiovascular imaging	
2D/3D transthoracic and transoesophageal echocardiography	(4D) ICE
CCT and CMR	
Cardiac surgery	
Access to expertise in valvular heart surgery, (including aortic valve replacement, mitral valve repair/replacement, tricuspid valve repair/replacement)	Heart transplantation and surgical circulatory support programme
Surgery on-site when investigational and replacement systems are used	
Electrophysiology service	
Expertise in CRT, pacemaker and ICD implantation, AF ablation	Expertise in lead extraction and repositioning, leadless pacemaker implantation
Intensive care unit	
Dedicated beds with invasive monitoring; expertise in management of patients in cardiogenic shock and requiring mechanical circulatory support	
Collaborative services	
Heart failure clinic	Extracardiac specialties: vascular surgery, neurology, nephrology, hepatology, and geriatrics
Data review	
Internal quality control	
Involvement in national and international databases	

2D: two-dimensional; 3D: three-dimensional; 4D: four-dimensional; AF: atrial fibrillation; CCT: cardiac computed tomography; CMR: cardiac magnetic resonance; CRT: cardiac resynchronisation therapy; ICD: implantable cardiac defibrillator; ICE: intracardiac echocardiography

FUTURE OUTLOOK AND CHALLENGES

Although TTVI are rapidly emerging in response to an unmet clinical need, some important questions remain largely unanswered and require rapid resolution by means of large-scale registies and randomised studies:

- symptomatic and outcome benefits of STR correction compared to optimal medical treatment (TRILUMINATE, CLASP II TR, and TRISCEND II pivotal trials; TRI-FR; TRICI-HF)
- the appropriate timing of intervention in relation to clinical status, severity of TR, RV function and pulmonary artery pressure

– criteria for concomitant or staged TTVI in conjunction with interventions for aortic and/or mitral valve disease
– comparative safety and efficacy of established and emerging transcatheter treatment options
– clinical and echocardiographic indicators to avoid futile interventions.

As a first priority, the wide variability of practice in relation to the diagnosis, assessment and timely management of TV disease should be addressed and unified across Europe, and programmes to increase awareness amongst primary and secondary care providers promoted.

Alongside the established VARC[95] and MVARC[96] criteria, the definition of standardised endpoints and definitions will ensure homogenous event reporting, accurate adjudication, and appropriate comparisons of clinical research studies involving new devices and therapeutic strategies for the treatment of TV disease. Given that endpoints of future studies are likely to be based largely on quality of life measures, levels of physical activity and assessement of volume status, new innovative concepts including wearable technology[97-99] and implantable HF monitoring devices will play an important role[100]. Since anatomical limitations, in particular large annulus size, still restrain eligibility, technological improvements are needed to address the needs of a broader population of patients. Advances in deep learning for the interpretation of echocardiographic, CCT and CMR images may further support standardisation and increase the accuracy of TR grading and assessement of RV function. These developments are set to accelerate rapidly in the next phase of the evolution of transcatheter valve interventions.

Appendix. Study collaborators.

Joao Cavalcante, MD, FASE, FACC, FSCCT, FSCMR; *Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, MN, USA*. Gilles Dreyfus, MD, FRCS, FESC; *Institut Mutualiste Montsouris, Paris, France*. Alison Duncan, MB BS, PhD, FRCP; *The Royal Brompton Hospital, London, UK*. Mara Gavazzoni, MD; *Cardiovascular Imaging Unit, Department of Cardiovascular, Neural and Metabolic Sciences, Instituto Auxologico Italiano, IRCCS, San Luca Hospital, Milan, Italy*. Julia Grapsa, MD, PhD, FACC; *Guy's and St Thomas' NHS Trust, London, UK*. Edwin Ho, MD, FRCPC; *Azeem Latib, MD, BCh; Montefiore Medical Center, New York, New York, USA*. Nicolo Piazza, MD, PhD; *McGill University Health Center, Montreal, Quebec, Canada*. Maurice Sarano, MD; *Mayo Clinic, Rochester, MN, USA*. Marta Sitges, MD, PhD; *Cardiovascular Institute, Hospital Clínic de Barcelona, Bacelona, Spain & University of Barcelona, Barcelona, Spain*. Martin Swaans, MD, PhD, FESC; *St. Antonius Hospital, Nieuwegein, the Netherlands*. Nina Wunderlich, MD, FACC; *Cardiovascular Center Darmstadt, Darmstadt, Germany*. Michel Zuber, MD, FESC; *Cantonal Hospital, Aarau, Switzerland*. Andrea Guidotti, MS; *Simulands Ltd, Zurich, Switzerland*. Scott Lim, MD; *University of Virginia, Charlottesville, VA, USA*. Chaim Lotan, MD, FACC, FESC; *Hadassah University Hospital, Jerusalem, Israel*. Thomas Modine, MD; *Cardiovascular Surgery Department, Cœur Poumon CHU de Lille, Lille, France*. Luis Ortega-Paz, MD, PhD; *Cardiovascular Institute, Hospital Clinic, IDIBAPS, Barcelona, Spain & Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL, USA*. Lars Sondergaard, MD; *The Heart Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*. Hendrick Treede, MD; *Department of Cardiac and Vascular Surgery, University Hospital Mainz, Johannes Gutenberg-University Mainz, Mainz, Germany*. Rudiger Lange, MD; *Department of Cardiovascular Surgery, German Heart Center Munich, Technische Universität München, Munich, Germany; Insure (Institute of Translational Cardiac Surgery), Department of Cardiovascular Surgery, German Heart Center Munich, Technische Universität München, Munich, Germany; DZHK (German Center for Cardiovascular Research) - Partner Site Munich Heart Alliance, Munich, Germany*. Marianna Adamo, MD; *Cardiac Catheterization Laboratory, ASST Spedali Civili di Brescia, Brescia, Italy*. Martin Andreas, MD, MBA, PhD, MEBCTS; *Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria*. Stephan Baldus, MD; *Department of Cardiology, University Heart Center, Cologne, Germany*. Paolo Denti, MD; *Progressive Cardiac Surgeon, San Raffaele University Hospital, Milan, Italy*. Nicolas Dumonteil, MD; *Clinique Pasteur, Toulouse, France*; Didier Tchétché, MD; *Clinique Pasteur, Toulouse, France*; Rodrigo Estevez-Loureiro, MD, PhD, FESC; *Interventional Cardiology Unit, University Hospital Alvaro Cunqueiro, Vigo, Spain*. Luigi Fiocca, MD; *Cardiovascular Department Papa Giovanni XXIII Hospital, Bergamo, Italy*. Kai Friedrichs, MD; *Herz- und Diabeteszentrum Nordrhein-Westfalen, Universitätsklinik der Ruhr-Universität Bochum, Bad Oeynhausen, Germany*. Carmelo Grasso, MD; *Cardio-Toraco-Vascular Department - CAST AOU Policlinico "G. Rodolico - S. Marco", Catania, Italy*. Nicole Karam, MD, PhD; *Université de Paris, PARCC, INSERM, F-75015, European Hospital Georges Pompidou, Paris, France*. Wolfgang Rottbauer, MD, PhD; *Department of Internal Medicine II (Cardiology, Angiology, Pneumology, Intensive Care Unit), Ulm University Medical Center, Ulm, Germany*. Volker Rudolph, MD; *General and Interventional Cardiology, Heart & Diabetes Center NRW, University Hospital of the Ruhr University of Bochum, Bad Oeynhausen, Germany*. Keti Vitanova, MD; *Department of Cardiovascular Surgery, German Heart Center Munich, Technische Universität München, Munich, Germany and Insure (Institute of Translational Cardiac Surgery), Department of Cardiovascular Surgery, German Heart Center Munich, Technische Universität München, Munich, Germany*. Jeroen Bax, MD, PhD, FESC, FACC; *Department of Cardiology, Leiden University Medical Centre (LUMC), Leiden, the Netherlands*. Michael Borger, MD, PhD; *University Clinic of Cardiac Surgery, Leipzig Heart Center, Leipzig, Germany*. Erwan Donal, MD, PhD; *University of Rennes, CHU Rennes, Inserm, LTSI - UMR 1099, Rennes, France*. Helge Möllmann, MD, PhD; *Department of Cardiology, St. Johannes Hospital, Dortmund, Germany*. Osama Soliman, MD, PhD, FACC, FESC; *Department of Cardiology, Saolta Group, Galway University Hospital, Health Service Executive and National University of Ireland Galway (NUIG), Galway, Ireland*. Maurizio Taramasso, MD, PhD, *HerzZentrum Hirslanden Zurich,*

Zurich, Switzerland. Holger Thiele, MD, FESC; *Heart Center Leipzig at University of Leipzig, Department of Internal Medicine/ Cardiology, Leipzig, Germany*. Nicolas van Mieghem, MD, PhD; *Department of Interventional Cardiology, Erasmus University Medical Centre, Rotterdam, the Netherlands*. Stephan Windecker, MD; *Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland*. Luigi Badano, MD, PhD; *Multimodality Cardiovascular Imaging Center, Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy & Department of Cardiology, Metabolic and Neural Sciences, San Luca Hospital, Istituto Auxologico Italiano, IRCCCS, Milan, Italy*. Manuel Barreiro, MD, PhD, FESC; *Cardiovascular Imaging, Cardiology Department, University Hospital Alvaro Cunqueiro, Vigo, Spain*. Lenard Conradi, MD; *University Heart and Vascular Center Hamburg, Department of Cardiovascular Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*. Neil Fam, MD MSc; *St. Michael's Hospital, University of Toronto, Toronto, Canada*. Xavier Freixa, MD, PhD; *Hospital Clinic of Barcelona. University of Barcelona. IDIBAPS. Barcelona, Spain*. Marco Metra, MD; *University and Civil Hospitals of Brescia, Brescia, Italy*. Gilbert Tang, MBA, MSc, MD; *Department of Cardiovascular Surgery, Mount Sinai Health System, New York, NY, USA*. Yan Topilsky, MD; *Cardiovascular Imaging, Cardiology Department, Tel Aviv Medical Center, Tel Aviv, Israel*. Alec Vahanian, MD; *University of Paris, Paris, France*. William Wijns, MD; *The Lambe Institute for Translational Medicine and Curam, National University of Ireland Galway, Galway, Ireland*.

Conflict of interest statement

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Supplementary data

Supplementary Table 1. Proposed expansion of the "severe" grade of TR.

Supplementary Table 2. Echocardiographic measures of RV size and function.

Supplementary Table 3. Specific tricuspid regurgitation aetiologies and specialised care.

Supplementary Figure 1. Steps to identifying tricuspid valve leaflets.

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00695

Supplementary data

Supplementary Table 1. **Proposed expansion of the "severe" grade of TR.**

Variable	Mild	Moderate	Severe	Massive	Torrential
VC (biplane)	<3 mm	3-6.9 mm	7-13 mm	14-20 mm	≥21 mm
EROA (PISA)	<20 mm^2	20-39 mm^2	40-59 mm^2	60-79 mm^2	≥80 mm^2
3D VCA or quantitative EROA*			75-94	95-114 mm^2	≥115 mm^2

* 3D VCA and quantitative Doppler EROA cut-offs may be larger than PISA EROA.

EROA: effective regurgitant orifice area; PISA: proximal isovelocity surface area; VC: vena contracta; 3D VCA, three-dimensional vena contracta area

Supplementary Table 2. Echocardiographic measures of RV size and function.

RV size parameter	**Mean±SD**	**Normal range**
RV basal diameter, mm	33±4	25-41
RV mid diameter, mm	27±4	19-35
RV longitudinal diameter, mm	71±6	59-83
RVOT PLAX diameter, mm	25±2.5	20-30
RVOT proximal diameter, mm	28±3.5	21-35
RVOT distal diameter, mm	22±2.5	17-27
RV EDV, mL/m² Men Women	 61±13 53±10.5	 35-87 32-74
RV ESV, mL/m² Men Women	 27±8.5 22±7	 10-44 8-36
RV wall thickness, mm	31	1-5
RV function parameter	**Normal range**	**Abnormal**
TAPSE, mm	24±3.5	<17
DTI S', cm/s	14.1±2.3	<9.5
Free wall LS, %	-29±4.5	>-20
RIMP (PW Doppler)	0.25±0.085	>0.43
RIMP (DTI)	0.38±0.08	>0.54
FAC, %	49±7	<35
RVEF, %	58±6.5	<45

DTI: Doppler tissue imaging; EDV: end-diastolic volume; ESV: end-systolic volume; FAC: fractional area change; LS: longitudinal strain; PLAX: parasternal long-axis view; PW: pulsed-wave; RIMP: right ventricular index of myocardial performance; RV: right ventricular; RVEF: right ventricular ejection fraction; RVOT: right ventricular outflow tract; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion

Supplementary Table 3. Specific tricuspid regurgitation aetiologies and specialised care.

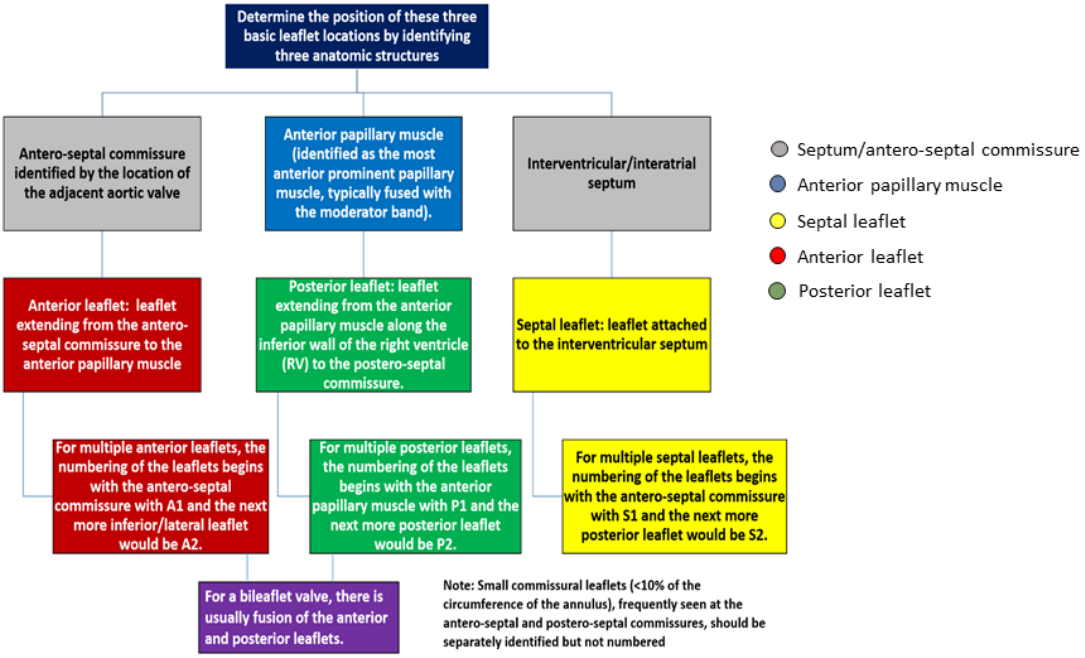
Phenotype	Mechanism of TR	Annular dilation	Leaflet tenting	Leaflet disease	Referral specialist	Diagnostic workup	Percutaneous treatment
Atrial fibrillation	Biatrial disease	+++	+/±	-/+	Electrophysiologist	Imaging*, RHC	Possible
Left-sided HF	Progression of cardiac dysfunction	++	++	-	Heart failure specialist	Imaging^, RHC	Possible
Left-sided valve disease	Primary valve disease/post-capillary pulmonary hypertension	++	++	+	Interventional cardiologist/ cardiac surgeon /echocardiographer	Imaging^, RHC	Possible
Pulmonary hypertension	Right ventricular dysfunction/remodelling	++	+++	-/±	Pulmonary hypertension centre Heart failure specialist/pneumologists/rheumatologist	Imaging, RHC	Unlikely
RV cardiomyopathy	Right ventricular dysfunction/remodelling	++	++	-	Heart failure specialist	Imaging, RHC	Possible
CIED related	Mechanical interference	±	-	±§	Electrophysiologist	Imaging, RHC	Sometimes possible
Primary TR	Tricuspid apparatus disease	+	-	+++	Cardiac surgeon/interventional cardiologist/echocardiographer	Imaging, RHC	Sometimes possible

* 2D, 3D and Doppler echocardiography; CCT

^ 2D, 3D and Doppler echocardiography; CCT and CMR in controversial cases

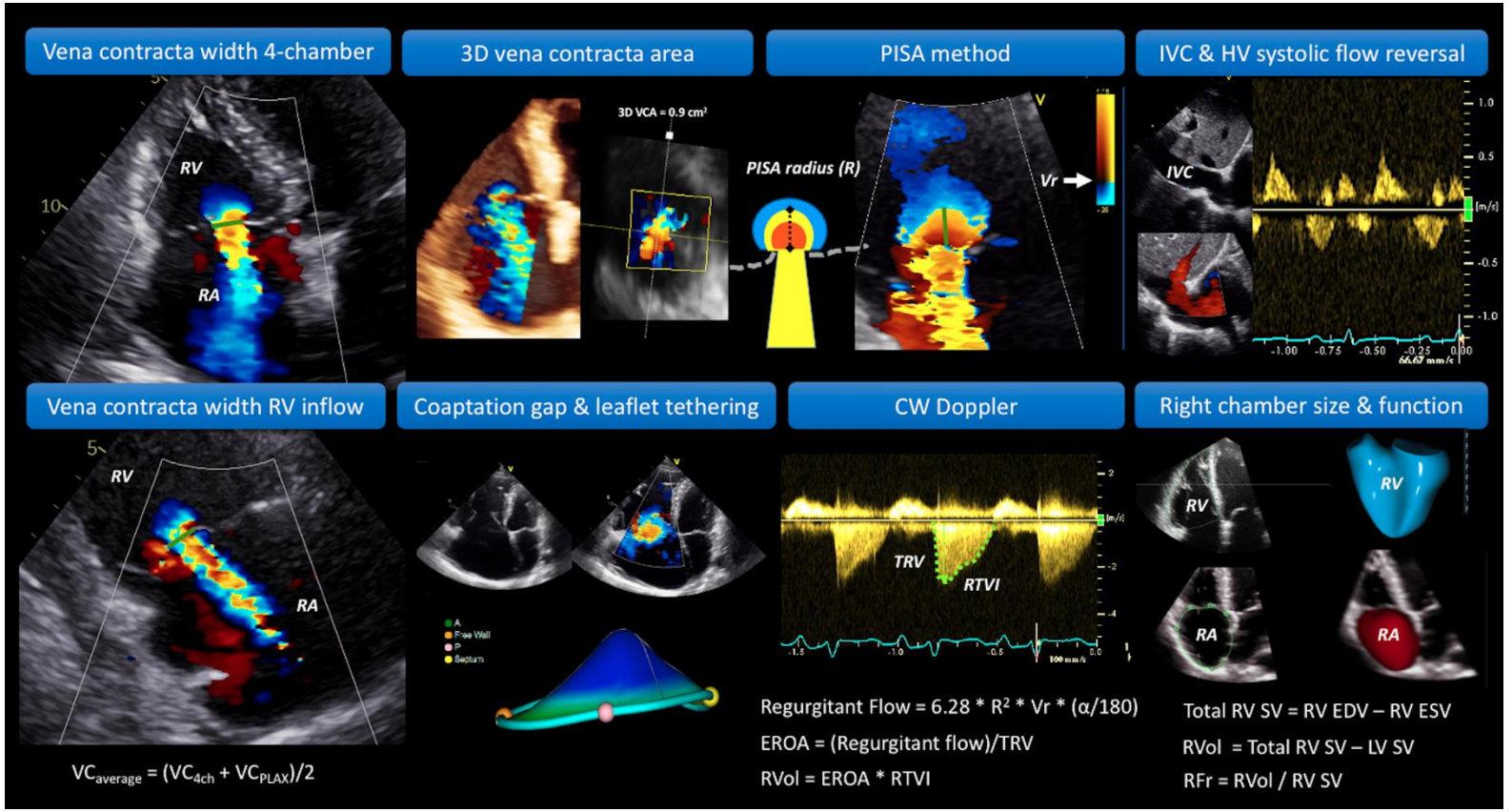
§ Depending on the mechanism (i.e., impinging vs entanglement vs perforation, etc.)

CIED: cardiac implantable electronic device; HF: heart failure; RHC: right heart catheterisation; RV: right ventricle; TR: tricuspid regurgitation



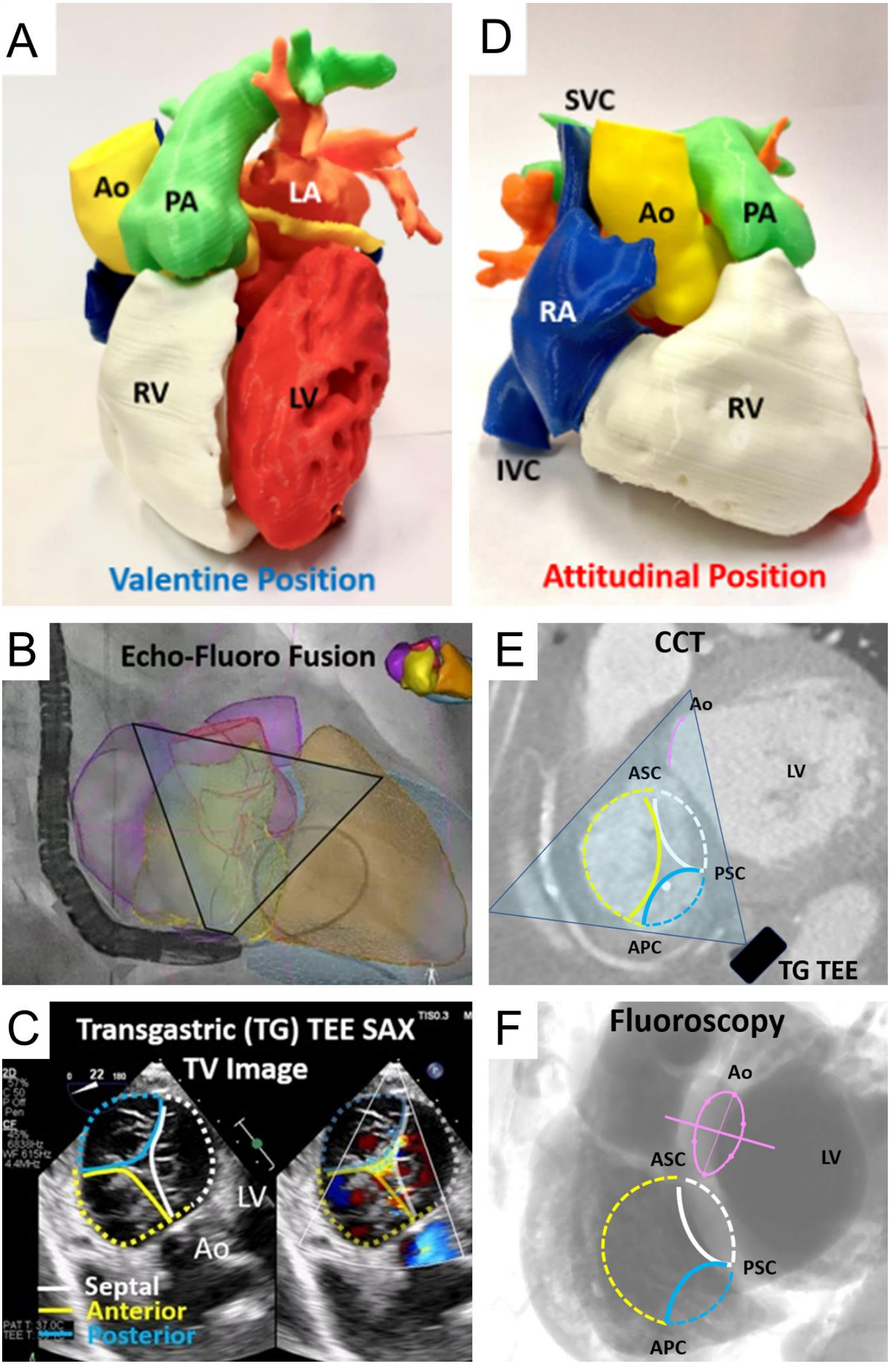
Supplementary Figure 1. Steps to identifying tricuspid valve leaflets.

Deep indentations and true commissures are considered anatomically equivalent and are used to identify supernumerary leaflets. A separate leaflet is defined by: (1) independent motion from the adjacent leaflet, and (2) colour Doppler systolic flow extending into the region around the leaflet. Four major classes of leaflet morphologies are possible. Colour-coding corresponds to Figure 1.



Supplementary Figure 2. Assessment of TR severity by Doppler echocardiography.

4ch: 4-chamber; EDV: end-diastolic volume; EROA: effective regurgitant orifice area; ESV: end-systolic volume; HV: hepatic vein; IVC: inferior vena cava; LV: left ventricular; PISA: proximal isolvelocity surface area; PLAX: parasternal long-axis; R: radius; RA: right atrium; RTVI: velocity-time integral of regurgitant jet; RV: right ventricle; SV: stroke volume; TRV: peak velocity TR jet; VC: vena contracta; VCA: vena contracta area; Vr: aliasing velocity


A
Ao
PA
LA
RV
LV
Valentine Position
D
SVC
Ao
PA
RA
RV
IVC
Attitudinal Position
B
Echo-Fluoro Fusion
E
CCT
Ao
ASC
LV
PSC
APC
TG TEE
C
Transgastric (TG) TEE SAX
TV Image
LV
Ao
Septal
Anterior
Posterior
F
Fluoroscopy
Ao
ASC
LV
PSC
APC

Supplementary Figure 3. Imaging and interventional perspectives of the tricuspid valve.

A) The traditional way to display the heart ("Valentine"), according to which the nomenclature of its structures derives from viewing the heart in an anterior orientation with the apex down.

B & C) Conventional nomenclature of the tricuspid leaflets (septal, anterior, posterior) applies for the conventional "Valentine" position and for transoesophageal echocardiographic (TEE) imaging when the probe is behind the heart.

D) Attitudinal position of the heart seen from the front as it lies on the diaphragm within the thorax, where the "right" chambers are anterior with respect to "left" chambers, the latter not being visible from this view.

E & F) According to attitudinal position, the nomenclature of the leaflets is: posterior (for septal), antero-superior (for anterior) and inferior (for posterior), according to their spatial position within the body, as depicted by CT (E) and fluoro images (F).

A: anterior; Ao: aorta; APC: anteroposterior commissure; ASC: anteroseptal commissure; CCT: cardiac computed tomography; IVC: inferior vena cava; LA: left atrium; LV: left ventricle; P: posterior; PA: pulmonary artery; PSC: posteroseptal commissure; RA: right atrium; RV: right ventricle; S: septal; SAX: short axis; SVC: superior vena cava; TEE: transoesophageal echocardiography; TG: transgastric; TV: tricuspid valve