

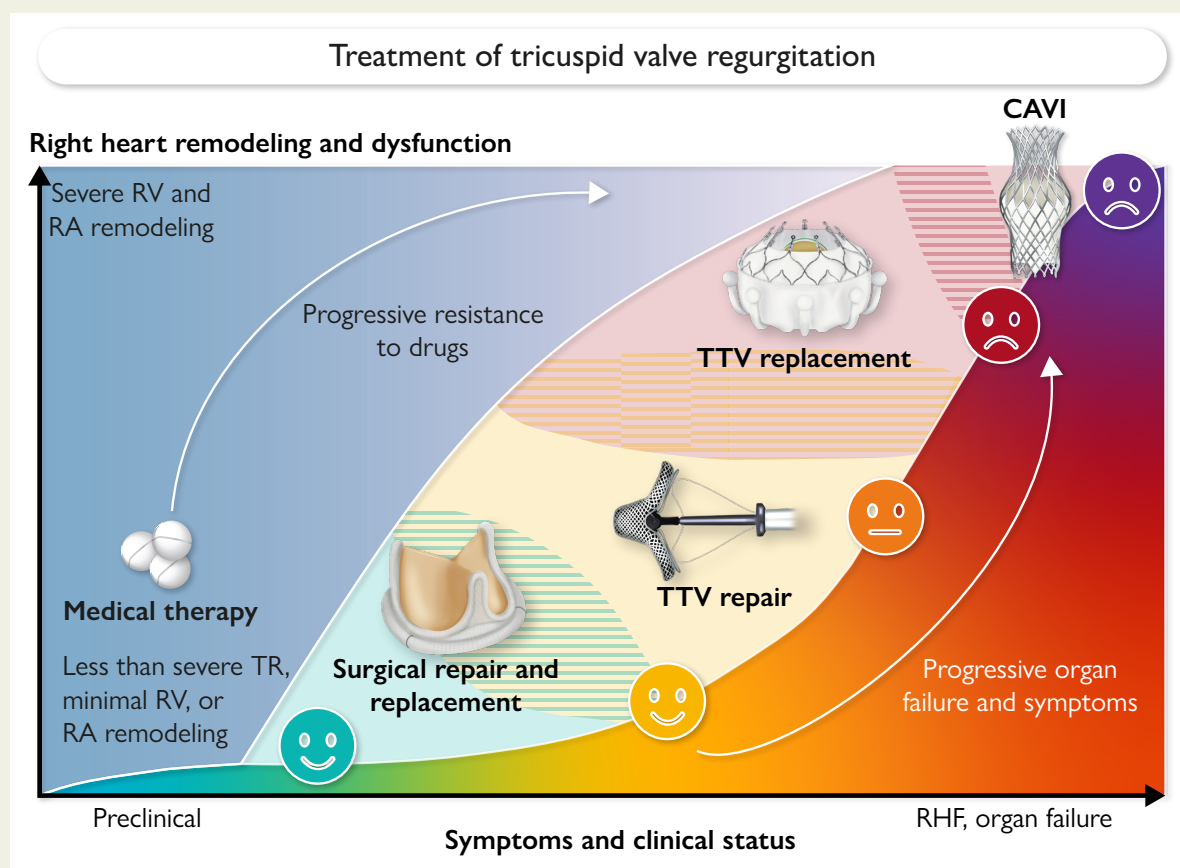
Transcatheter treatment of the tricuspid valve: current status and perspectives

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Graphical Abstract



Disease stage and therapeutic strategies for tricuspid regurgitation. Tricuspid regurgitation evolves from undetectable early forms to advanced stages characterized by escalating symptoms, right heart failure, and organ impairment. While medical therapy is utilized throughout the disease course, its effectiveness wanes with progression. Surgery can play a role in the earlier stages, while transcatheter therapies are available for patients at high risk and in the more advanced stages of disease. Significant overlap between treatment options underscores the urgent need for precise, evidence-based

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protocols. Overall, early intervention is crucial to prevent organ damage and avoid futility of late treatments (smileys becoming sad). CAVI, caval valve implantation; RHF, right heart failure; TR, tricuspid regurgitation; RA, right atrial; RV, right ventricular; TTV, transcatheter tricuspid valve.

Abstract

Transcatheter tricuspid valve interventions (TTVI) are emerging as alternatives to surgery in high-risk patients with isolated or concomitant tricuspid regurgitation. The development of new minimally invasive solutions potentially more adapted to this largely undertreated population of patients, has fuelled the interest for the tricuspid valve. Growing evidence and new concepts have contributed to revise obsolete and misleading perceptions around the right side of the heart. New definitions, classifications, and a better understanding of the disease pathophysiology and phenotypes, as well as their associated patient journeys have profoundly and durably changed the landscape of tricuspid disease. A number of registries and a recent randomized controlled pivotal trial provide preliminary guidance for decision-making. TTVI seem to be very safe and effective in selected patients, although clinical benefits beyond improved quality of life remain to be demonstrated. Even if more efforts are needed, increased disease awareness is gaining momentum in the community and supports the establishment of dedicated expert valve centres. This review is summarizing the achievements in the field and provides perspectives for a less invasive management of a no-more-forgotten disease.

Keywords Tricuspid regurgitation • Right heart • Heart failure • TTVI • Transcatheter interventions • Percutaneous • Repair • Replacement

Incipit: 'In the delicate chambers of the heart, where life's symphony finds its rhythm, a silent trouble lingers. A tricuspid valve, once a guardian of harmony, now whispers a discordant tune, signaling the presence of a hidden disease...'

Anonymous Chatbot

The recent introduction of transcatheter tricuspid valve interventions (TTVI) has dramatically influenced the perception of the relevance of tricuspid valve (TV) disease. As more evidence becomes available, concepts and strategies are evolving ([Graphical Abstract](#)) and new challenges emerge in the quest to uncover the secrets of the right side of the heart. This state-of-the-art review is revisiting TV disease through the most up-to-date knowledge of its mechanisms, diagnostics, and treatment options, bringing to light the valve that is anything but forgotten.

Tricuspid valve regurgitation: a no-more-forgotten entity

The TV has long been disregarded and as a result remained relatively under-studied, leading to under-recognition, and under-treatment. For more than 50 years, tricuspid regurgitation (TR) has been classified as a signal rather than a causative prognostic factor, believed to be easily reversible with treatment of left heart disease, or surrogate of end-stage disease indicating an inoperable condition. Nina Braunwald, in a publication considered the manifesto of the 'forgotten valve', described TR as a secondary issue, 'seldom requiring an intervention'.¹ Several factors supported the theory that the right circulation is less impactful on survival than the left. As an example, children with surgically corrected congenital heart disease have survived with univentricular physiology. TV endocarditis has been treated with valvectomy with acceptable short-term results.² In addition, diuretics can efficiently control symptoms of venous congestion and reduce the degree of TR.³ In the setting of nonspecific signs and symptoms as well as early diuretic responsiveness, there has been a tendency to delay interventions. Surgery for isolated TR has been associated with debatable prognostic impact⁴ and high in-hospital mortality,⁵

possibly related to the late referral but also influencing referral rates for this procedure.

Recent evidence challenges the belief that TV disease and, overall, right heart (RH) failure are of 'secondary' importance. In addition, recent advances in valvular interventions have broadened the spectrum of treatable patients to high risk or inoperable patients. The broad range of transcatheter treatment eligible patients, as well as less invasive nature of the procedures, will allow us to study the effect of TR reduction on prognosis and quality of life (QoL), but also, and probably more importantly, advance our understanding of the interaction between TV function and RH physiology, improving our detection of adaptive and maladaptive processes.

The burden of a misleading disease: from marker to culprit

The role of TR as a marker of disease severity is unquestioned. The development of TR as a consequence of left heart disease or pulmonary hypertension (PH) is associated with worsening prognosis in congestive heart failure,⁶ primary PH,⁷ and in patients undergoing aortic^{8,9} or mitral valve interventions.^{10–12} However, the absolute impact of isolated TR on prognosis has been long questioned. In addition, symptoms of isolated severe TR can be highly misleading and underestimated during its early stages or confounded with other conditions, particularly in the elderly. In a recent study, asthenia, ankle swelling, abdominal pain or distention, and/or anorexia have been found to be predictive of clinical outcomes in patients with TR.¹³ With an aging population and improved left heart failure management, the prevalence of TR is increasing and these unconventional symptoms are red flags motivating further investigations.

The Framingham study reported a prevalence of 1.5% in men and 5.6% in women of at least moderate TR in the elderly (above 70 years) population.¹⁴ A more recent community-based prospective study showed that 16% of patients ≥65 years old had previously undiagnosed moderate or severe valvular heart disease, with TR having the highest prevalence at 7.2%,¹⁵ confirming the Framingham study. According to the Eurostat census, in 2001 there were 54 million elderly inhabitants in Europe, of which 21 million were male and 34 were million female

Table 1 New classification of TR according to mechanism and aetiology

	Mechanism of regurgitation	aetiology	Main imaging and staging	Typical patient journey (referral clinics)
Secondary (functional) tricuspid regurgitation				
Valve structures are anatomically normal, valve dysfunction is secondary to atrial or ventricular remodelling and dysfunction				
Ventricular TR	TR due to a combination of annular dilatation and leaflet tethering caused by RV remodelling and/or dysfunction	Pulmonary hypertension Left heart valvular disease HFrEF, HFpEF Right ventricular infarction Right ventricular cardiomyopathy Congenital anomalies	2D/3D echocardiography for TR grading, quantification of valve and ventricular remodelling, RV systolic function RH catheterization Biomarkers	Heart Failure clinic Cardiovascular surgery Pneumology GUCH
Atriogenic TR	TR is mainly driven by annular dilatation and dysfunction. Normal RV function and shape (conical shape preserved)	Atrial fibrillation HFpEF Aging	2D/3D echocardiography for TR grading, quantification of valve and ventricular remodelling, RV systolic function RH catheterization Biomarkers	Electrophysiology General cardiologist Family physician Internal Medicine Heart Failure clinic
Primary or mixed tricuspid regurgitation				
Valve structures are abnormal				
Primary	Chordal elongation/rupture Papillary muscle rupture (trauma) Excessive leaflet motion (myxomatous disease) Leaflet perforation (endocarditis) Leaflet retraction (rheumatic, inflammatory diseases)	Endocarditis Myxomatous disease Rheumatic disease Trauma NET tumours	2D/3D echocardiography for TR grading, quantification of valve and ventricular remodelling, RV systolic function	Internal medicine Infectiology Traumatology General Cardiologist Gastroenterology
CIED-related				
TR is caused by the interaction with intracavitary leads				
CIED-related	Leaflet impingement, chordal entanglement or rupture, leaflet adherence, perforation, laceration (post-extraction)	Implant of an intracardiac electrical device crossing the tricuspid valve. Implant of a leadless pacemaker Lead extraction	EP evaluation 2D/3D echocardiography for TR grading, quantification of valve and ventricular remodelling, RV systolic function Assessment of lead influence: CIED-related vs. CIED-associated TR)	Electrophysiology Heart failure clinic

The existence of multiple tricuspid regurgitation phenotypes, each with distinct regurgitation mechanisms and patient trajectories, indicates the necessity for personalized care strategies. This encompasses everything from diagnostic and therapeutic approaches to ongoing lifetime management.

RV, right ventricular; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; NET, neuroendocrine tumours; RH, right heart; EP, electrophysiology; CIED, cardiac implantable electronic device; GUCH, grown-up congenital heart disease; TR, tricuspid regurgitation.

(https://ec.europa.eu/eurostat/databrowser/view/CENS_HNMGA__custom_6714995/default/table?lang=en). This would predict a potential population of 2.2 million individuals with at least moderate TR in Europe. Topilsky et al., in a population-based registry, found a 0.55% prevalence of at least moderate TR in the overall population, which increased with age and in women.¹⁶ The most common cause of TR was left heart disease (valve disease or left ventricular dysfunction) and PH, while isolated, non-primary, TR was found in 8% of the population. The overall survival under medical management in patients with isolated TR was inferior to that of matched individuals with trivial TR (hazard ratio -HR-¹⁵ 1.17; $P = .01$). Nath et al. reported an increased mortality risk [adjusted for age, left ventricular ejection fraction, inferior vena cava (IVC) size, and right ventricular (RV)¹⁶ size and function] with moderate (HR 1.17) and severe TR (HR 1.31) in a retrospective analysis of 5223 patients.¹⁷

Data from the UK Biobank showed that, compared to patients with no valvular heart disease, the risk of all-cause death is more than 2.5 times higher for TR.¹⁸ This is supported by a large population study of the National Echocardiography Database of Australia on 439 558 patients referred to echocardiographic examination¹⁹ that revealed a prevalence of moderate and severe TR of 5.9% and 1.8%, respectively. Following adjustment for RV systolic pressure, atrial fibrillation, and left heart disease, severe TR was associated with 2.65 increased risk of mortality. Interestingly, increased risk was observed also in patients with mild (HR 1.24), or moderate TR (HR 1.72). Wang et al.²⁰ performed a systematic review and meta-analysis suggesting that TR is associated with increased mortality independently of pulmonary pressures and RH failure. The risk of mortality at a mean follow-up of 3.2 ± 2.1 years increased from 1.25 to 1.61 and 3.44-fold in patients

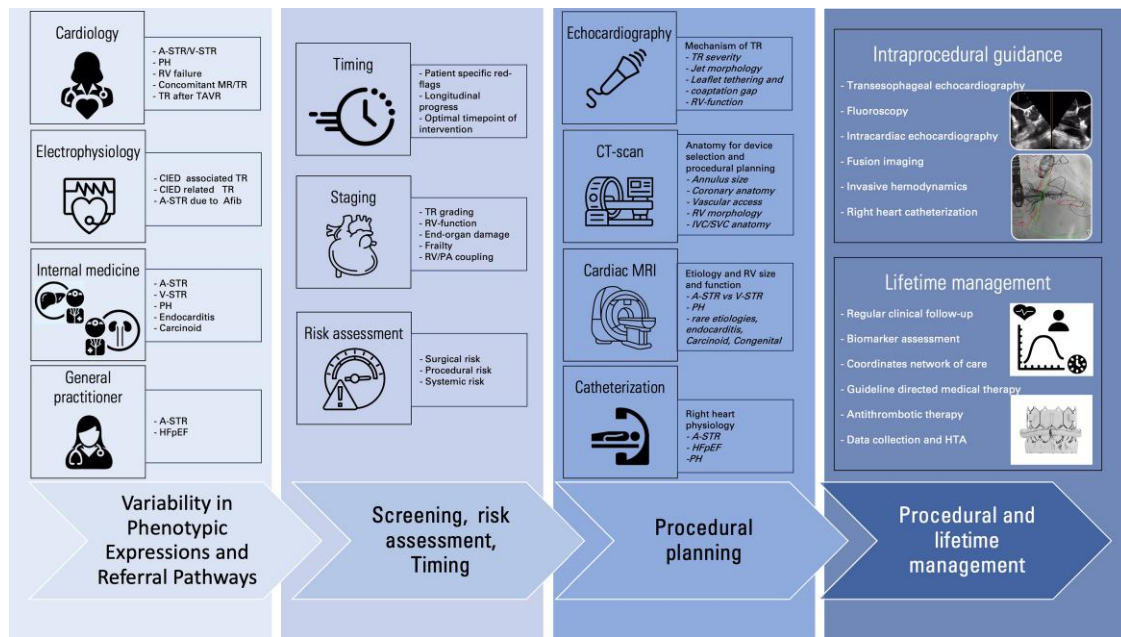


Figure 1 Patient journeys across different tricuspid regurgitation phenotypes. Patients with significant tricuspid regurgitation come from diverse disease journeys and may be referred to the Valve Team by different specialists. Following screening and risk stratification, if tricuspid regurgitation is deemed suitable for treatment, comprehensive multimodal imaging is essential for choosing the appropriate device, planning the procedure, and guiding the intervention. Post-intervention, patients enter a lifelong care program within a network that emphasizes seamless continuity of care and ongoing evaluation of their health outcomes. Abbreviations: A-STR, atrial secondary tricuspid regurgitation; V-STR, ventricular secondary tricuspid regurgitation; PH, pulmonary hypertension; RV, right ventricular; MR, mitral regurgitation; TR, tricuspid regurgitation; TAVR, transcatheter aortic valve replacement; CIED, cardiac implantable electronic device; Afib, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; PA, pulmonary artery; IVC, inferior vena cava; SVC, superior vena cava; HTA, health technology assessment

with mild, moderate, or severe TR, respectively. Patients with at least moderate TR had an overall 2.56-fold increased cardiac mortality and a 1.73-fold increased heart failure hospitalization rate.

These data challenge the misconception that TR is a benign condition and suggests us to refer patients presenting with at least moderate TR to a valve centre with dedicated expertise for further risk stratification and management.

Revised definitions unveiling different phenotypes and patient journeys

TR disease can develop under diverse circumstances, leading to a wide spectrum of phenotypes with different mechanisms and aetiology. The PCR Focus group (<https://www.pcronline.com/Network/Tricuspid-Focus-Group>) revised the TR classification^{21,22} (Table 1) subdividing the formerly called functional TR into atrial secondary TR (A-STR) or ventricular secondary TR (V-STR), while primary TR encompasses a variety of subsets ranging from congenital malformation, traumatic lesions to endocarditis. Cardiac implantable electronic device (CIED)-related TR is considered a separate entity with distinctive disease mechanisms and management. In addition to the variability of valve morphology, mechanisms of regurgitation, and hemodynamics, clinical presentation seems to have prognostic relevance. This suggests different patient journeys and referral pathways (Figure 1). As an example,

prognosis of A-STR treated conservatively²³ or following an intervention²⁴ is more favourable as compared to patients with V-STR, while the impact of TR treatment in patients with fixed pre-capillary PH is debatable. Such variability deserves further investigation and targeted therapies for a tailored approach. Recently, a comprehensive risk stratification based on pheno-clusters including aetiology and clinical presentation has been proposed.²⁵ RH function plays a major role in risk assessment with signs of RV failure indicating later stages of disease progression.^{26,27}

Risk scores for assessing short-term mortality both for medically treated²⁸ and surgically treated²⁹ patients have included both RV function and RH failure symptoms, in addition to a number of other clinical and laboratory parameters (Figure 2).

Function follows morphology, and in the spectrum of TR subsets, the anatomic-functional presentation of the valve and of the RH is highly variable.³⁰ Different mechanisms of regurgitation and disease progression imply the need for different types of interventions. Recent advances in three-dimensional (3D) echocardiography and the use of tomographic imaging modalities allow a comprehensive investigation of the morphology of the valve apparatus and guide device selection for valve repair and replacement.

All the components of the valve apparatus play a role: leaflet and sub-valvar apparatus distribution, annular shape and function, as well as right atrial³¹ and ventricular³² function and morphology. To challenge the current nomenclature, TV has rarely three leaflets. Almost half of the valves with TR have more than three leaflets. This finding is highly relevant for leaflet devices, such as Triclip (Abbott Vascular, Menlo Park, CA,

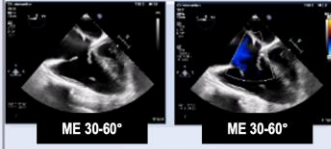
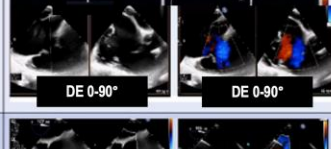
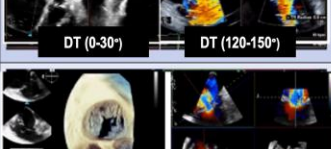
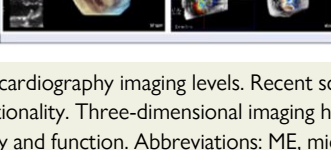
View	Imaging examples	Structures imaged	Potential role in procedural guidance
4-Chamber view, ME (0-30°)		- Tricuspid valve (A, S) - Right atrium/right ventricle/outflow - Left atrium/ventricle - Aortic valve	Septal and anterior tricuspid valve leaflets (for TEER) and annulus (for annular or replacement 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 (0-90°) Short-Axis view TG (100-130°)		- 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 3 Transesophageal echocardiography imaging levels. Recent screening guidelines recommend a standardized imaging protocol for evaluating tricuspid valve structure and functionality. Three-dimensional imaging has become integral to the detailed assessment of the tricuspid valve, providing critical insights into its morphology and function. Abbreviations: ME, mid-esophageal; RV, right ventricular; DE, deep esophageal; TG, transgastric; DT, deep transgastric; SAX, short axis; A, anterior; P, posterior; S, septal; TEER, transcatheter edge-to-edge repair

papillary muscles). These anatomic parameters support optimal patient-specific device selection. Multi-modality imaging has also become the standard for the assessment of procedural eligibility.³⁴ Computed tomography (CT) allows comprehensive anatomical evaluation of the TV complex, right ventricle, and right coronary artery. In addition, CT is essential for pre-procedural planning of device delivery. Device-specific evaluation may include assessment of femoral or jugular vein diameters, cavo-atrial angulation, or detailed evaluation of caval anatomy.^{42,43} Although currently underutilized for TR, cardiac magnetic resonance (CMR) imaging is helpful to quantify TR in case of discrepant echocardiographic findings⁴⁴ and is the reference method to quantify RV size and function.^{41,45}

Intra-procedural imaging relies primarily on TEE and fluoroscopy.^{34,46,47} New TEE screening guidelines have standardized TV imaging⁴⁸ and improved intra-procedural imaging protocols⁴⁶ (Figure 3). The use of echo-fluoro fusion imaging may improve intra-procedural communication between operators by the fusion of two modalities from nearly orthogonal points of view.²¹ The recent introduction of

3D intracardiac echocardiography (ICE) catheters already had a significant impact on TTVI technical success when TEE is suboptimal.^{49–52} Both TEE and ICE catheters have biplane imaging with both lateral and elevational tilt, and live 3D multi-planar reconstruction (MPR) which allows simultaneous visualization of three different (often orthogonal) 2D images, in addition to the 3D volume. Because of the innumerable ways in which the images can be manipulated, a dedicated, trained interventional imager is required for both TEE and ICE imaging during TTVI.³⁸

Current treatment options: guidelines and real-world

The 2021 ESC/EACTS valvular heart disease guidelines recommend that interventional treatment of secondary TR may be considered in experienced Heart Valve Centers in symptomatic but inoperable patients, who are anatomically eligible and have the potential for a clinical

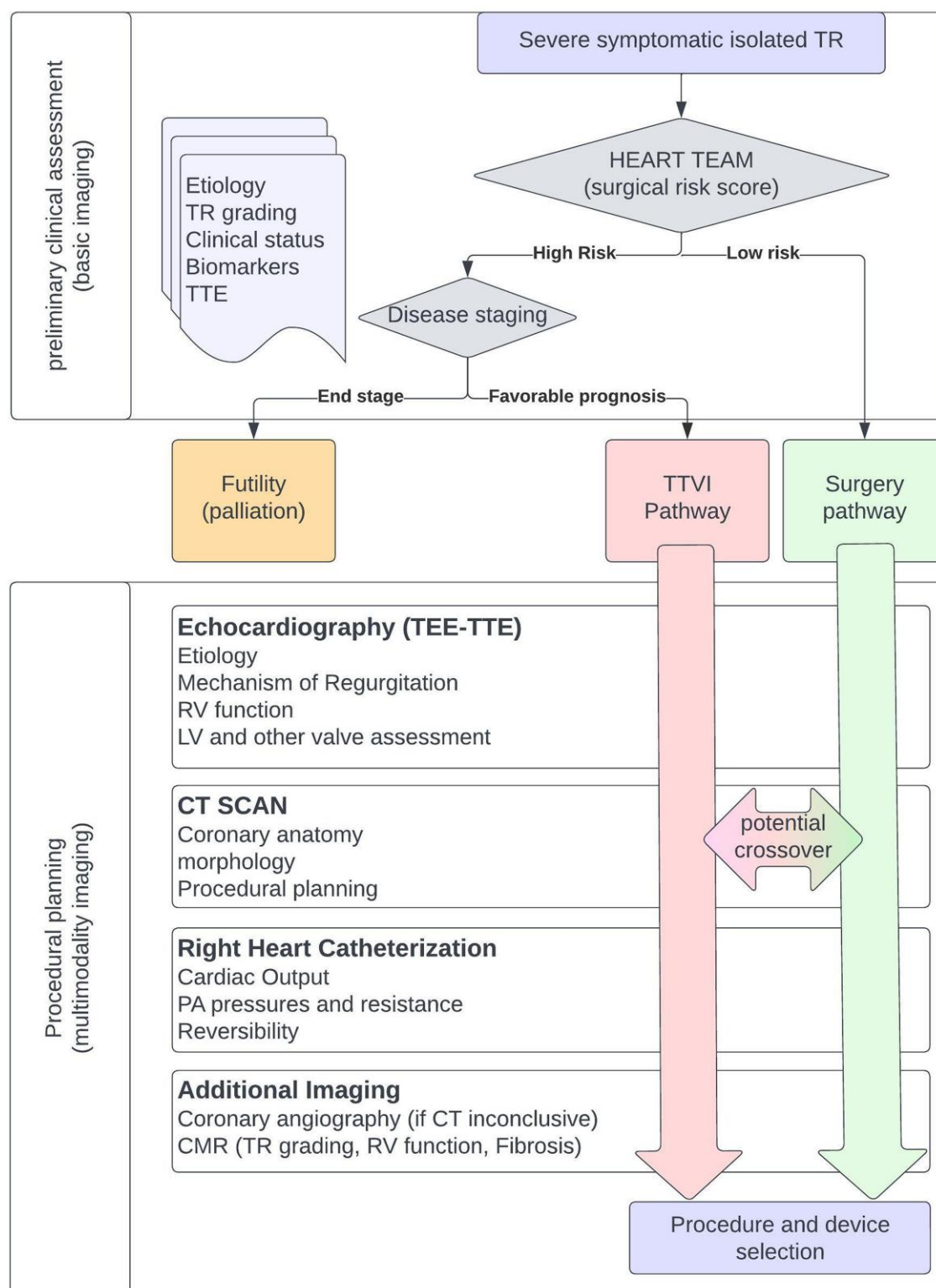


Figure 4 Imaging protocols for in-hospital tricuspid regurgitation screening and treatment planning. For patients with severe symptomatic tricuspid regurgitation, initial screening combines basic imaging techniques, predominantly transthoracic echocardiography, and right heart catheterization, with clinical assessments to stage the disease. Intervention candidates, whether for transcatheter or surgical approaches, require further comprehensive multimodal imaging to tailor the optimal treatment strategy and to support procedural and device selection

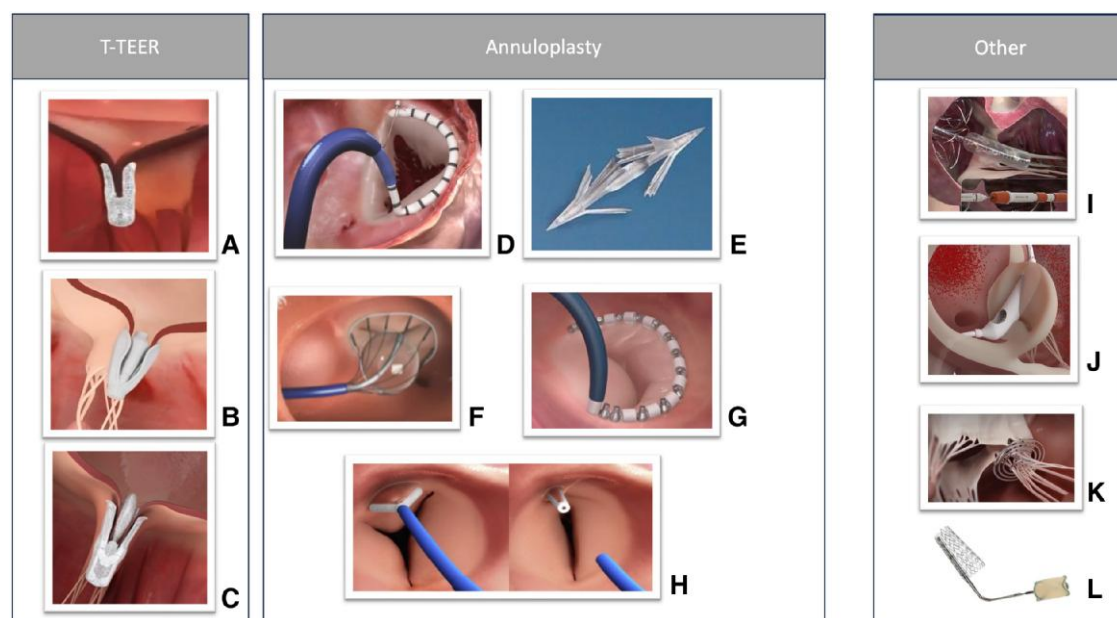


Figure 5 Repair technologies approved for clinical use in Europe or actively under investigation. (A) Triclip (CE marked); (B) PASCAL (CE marked); (C) Dragonfly; (D) Cardioband (CE marked); (E) MIA-T; (F) Cardiac Implants Tri-Ring; (G) Dragon Ring; (H) F-clip; (I) Coramaze; (J) PivotTR; (K) Mitrelx; (L) Croivalve Duo

benefit from the procedure.⁵³ While the exact timing for the procedure in both symptomatic and asymptomatic with RH dilation is still matter of debate, earlier referral is beneficial and supported by guidelines. As far as TTVI should be reserved for inoperable patients, surgical risk should be assessed using specific risk scores. The common simplification that surgery is high risk, should be demystified. Overall surgical risk in the Society of Thoracic Surgeons database is ~7%. However, hospital mortality is highly dependent on the disease stage and indication of treatment, being highest in patients with right-sided infective endocarditis.⁵⁴ When surgery is performed at earlier stages, mortality for isolated TR can be minimized.⁵⁵ The TRI-SCORE registry developed an additive scoring method to predict hospital mortality in patients undergoing surgery for isolated TR (Figure 2).²⁹ Lacking a reliable method to avoid futility, data from real-world registries^{56–58} as well as local experience within the Heart Team should guide decisions within the in-hospital pathway (Figure 4).

Transcatheter valve repair techniques

Valve repair can be achieved with leaflet approximation devices, with annuloplasty, or with other devices including ‘spacers’ (devices filling the coaptation gap) and chordal approximation devices (Figure 5). The first transcatheter tricuspid valve repair (TTVr) has been performed with the MitraClip system (Abbott Vascular Inc, Santa Clara, CA, USA) in a corrected transposition patient with a morphologically tricuspid left atrio-ventricular valve.⁵⁹ Initially, tricuspid transcatheter edge-to-edge repair (T-TEER) with off-label MitraClip was broadly performed in Europe, usually as an adjunct to mitral interventions. To-date, T-TEER remains the most commonly performed TTVr procedure, with two approved devices. The TriClip is a dedicated multi-steering delivery

system optimized for T-TEER, while PASCAL can be used indifferently for both atrio-ventricular valves. Both feature T-TEER devices of different sizes to accommodate for diverse leaflet anatomies and jet locations. The TriClip device features implants of four different sizes with an active closing mechanism. The most used device is the XTW, the longest and larger clip size, maximizing the amount of potential annular reduction.⁶⁰ The fourth-generation device allows independent grasping and continuous pressure monitoring. The PASCAL system is a nitinol-based device with a passive closing mechanism, incorporating two paddles and a spacer to fill the coaptation defect. The device has a unique elongation feature that minimize the risk of leaflet entanglement. Two sizes are available and continuous pressure monitoring is integrated in the steerable catheter. Additional devices are in early feasibility development and initial clinical trials. The Dragonfly⁶¹ (Venus Medtec, Hangzhou, China) system is currently under first-in-man evaluation in China.

T-TEER addresses TR by a combination of leaflet approximation at the site of regurgitation and indirect annular reduction. Initial efforts have been challenged by anatomical complexity, lack of dedicated devices, and intra-procedural imaging complexity. Initially, most implants were confined in the antero-septal commissure, because of the ease of approach and visualization by TEE. The antero-septal coaptation line remains the main initial target, trying to approximate leaflet in the centre of the valve. The clover technique requires an additional device in the postero-septal coaptation line^{62,63} to maximize leaflet approximation and annular reduction.⁶⁰ Safety and efficacy of T-TEER have been shown in several single-arm registries^{64–67} and recently confirmed in pivotal trials.⁶⁸ The improvement of clinical outcomes follows TR reduction,^{57,68} while the ideal cut-off for residual gradients remains debated.⁶⁹ Few non-randomized comparisons between devices show very comparable outcomes.⁷⁰ Several predictors of procedural success have been found. The

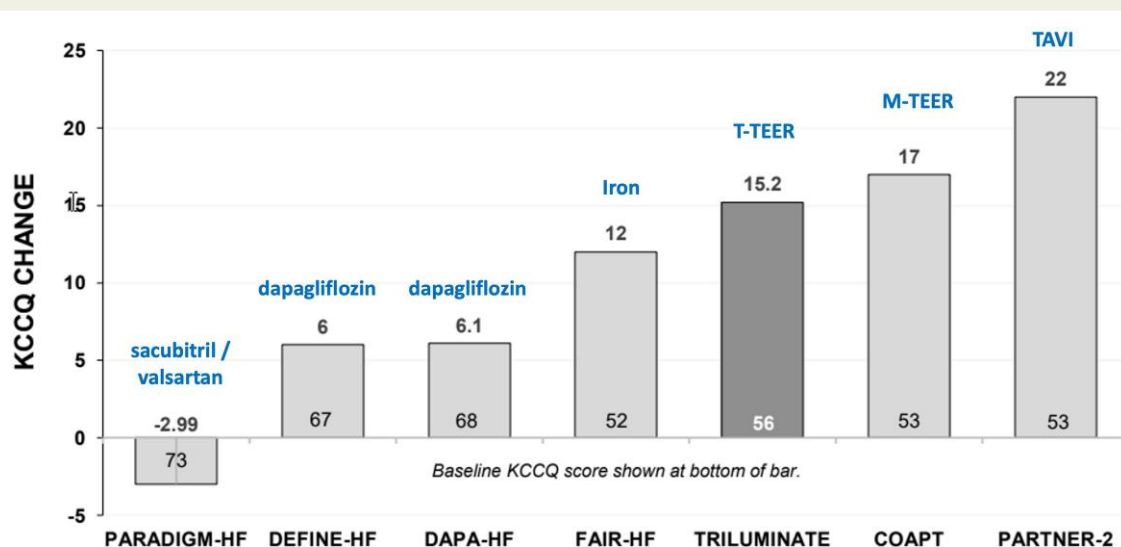


Figure 6 Quality of life improvement (as assessed by Kansas City Cardiomyopathy Questionnaire) in various heart failure randomized controlled trials. The quality of life improvements reported in the TRILUMINATE trial align with those seen in other structural heart disease studies and exceed the enhancements typically noted in heart failure drug trials. In these trials, various interventions were evaluated: sacubitril/valsartan in PARADIGM-HF;¹⁰³ dapagliflozin in DEFINE-HF¹⁰⁴ and DAPA-HF,¹⁰⁵ intravenous ferric carboxymaltose in FAIR-HF;¹⁰⁶ the MitraClip procedure for secondary mitral regurgitation in COAPT,¹⁰² and transcatheter aortic valve implantation for intermediate-risk patients in PARTNER 2.¹⁰⁷

main anatomical determinants are the leaflet coaptation gap and the non-central or non-anteroseptal location of the jet.^{71,72} A threshold for coaptation gap defining ineligibility for TEER is debatable, due to its load dependency. Leaflet-to-annulus index⁷² is a promising alternative, derived from mitral interventions.^{73,74} Complex valve morphologies, with multiple leaflets, in isolation,³³ or in combination with larger gaps,⁷⁵ are associated with residual TR. T-TEER is feasible in selected patients with CIED leads with short-term clinical outcomes comparable to patients without lead.⁷⁶

Short and long-term outcomes are strongly affected by aetiology,⁷⁷ clinical presentation,⁷⁸ RH hemodynamics,^{79,80} comorbidities, organ reserve, and stage of the disease.⁸¹ Recent registries show an overall improvement in safety and efficacy of T-TEER even in anatomically challenging scenarios. In the post-approval bRIGHT post-approval study using the fourth-generation TriClip system, most patients were highly symptomatic [New York Heart Association (NYHA) class III–IV] and had more than severe TR. In this unselected population, hospital mortality and rate of adverse events were as low as 1% and 2.5%, respectively. Procedural success (reduction to $\leq 2+$ TR) was obtained in 77% of patients, with early improvement of symptoms and QoL. Predictors of success were smaller tethering distance and smaller right atrial volumes at baseline.⁵⁸ Similarly, the CLASP TR trial reported a 3.1% 30 day-mortality, and sustained 1-year TR reduction (86% achieving $\leq 2+$ TR),⁸² associated with improved QoL and symptoms and comparable results were reported in the PASTE post-market registry including more than 230 patients.⁶⁶

While T-TEER is the most performed intervention, annuloplasty replicates the most common surgical repair procedure, with the peculiarity of leaving all alternative options open. Cardioband system was the first TTVI device approved in Europe.⁸³ Cardioband is implanted under echocardiographic guidance with multiple anchoring screws, followed by echo-guided annular reduction. The TRI-REPAIR observational study enrolled 30 patients with

symptomatic functional TR.⁸⁴ At 2 years, echocardiography showed a 16% reduction in septolateral annular diameter, and $\leq 2+$ TR in 72% of patients. Six-minute walking distance and Kansas City Cardiomyopathy Questionnaire (KCCQ) score improved by 73 m and 14 points, respectively. Despite its strong rationale, Cardioband is implanted only in very experienced centres, because of the complexity of the procedure, and the potential risk of coronary lesions.⁸⁵ For the same reasons, several other direct and indirect annuloplasty devices have been discontinued or are in the early feasibility stage.^{47,86–100} Second-generation devices are expected to simplify the procedure. The minimal effect on valve gradients, the minimal footprint of the implant, and the possibility of combining leaflet and annular repair imitating surgery¹⁰¹ warrant further efforts in this field.

Emerging randomized controlled evidence: the impact of TR treatment

Although registries are key to explore the safety and feasibility of interventions, the fundamental question of whether TR treatment can influence survival remains to be answered. A propensity-matched analysis comparing survival of patients undergoing TTVI to a historical series of medically treated patients suggested a potential survival benefit in patients who received successful treatment.⁵⁶

The TRILUMINATE pivotal trial⁶⁸ has a historical significance since it is the first randomized study investigating an isolated TR treatment strategy compared to medical therapy alone. The trial randomized 350 symptomatic patients with severe TR with a hierarchical composite primary endpoint at 1 year consisting of death or TV surgery, heart failure hospitalization, and improvement in QoL as measured with the KCCQ. A minimal 15 KCCQ points improvement was considered

Table 2 Comparison between the TRILUMINATE cohort and 'real-world' data from registries

	TRILUMINATE RCT arm (TriClip) n = 350	bRIGHT Study (TriClip) n = 511	PASTE Registry (PASCAL) n = 603	TRISCEND I (EVOQUE) n = 176
Demographics				
Age, years, mean $\pm$ SD	77.9 $\pm$ 7.3	78.9 $\pm$ 7.1	78 $\pm$ 9	78.7 $\pm$ 7.33
Male/female sex	45%/55%	44%/56%	47%/53%	39%/71%
Medical history				
NYHA class III/IV at baseline	57.5%	80%	89%	75.4%
Prior permanent pacemaker implantation	14.9%	22.5%	28%	32.4%
KCCQ score at baseline, mean $\pm$ SD	55.1 $\pm$ 23.8	44.5 $\pm$ 22.6		46.0 $\pm$ 21.8
Prior heart failure hospitalization lasts 12 months	25.1%	40.3%		40.9%
Baseline TR grade				
Moderate	1.8%	2.0%	6%	12.5%
Severe	27.5%	10.0%	38%	44.7%
Massive/torrential	70.7%	88%	56%	42.8%
Key procedural data				
Coaptation gap, mm, mean $\pm$ SD	5.4 $\pm$ 1.8	6.5 $\pm$ 2.7	6.3 $\pm$ 3.4	
TR $\leq$ moderate at 30 days	87%	77%	81%	100%
SLDA rate	7.0%	3.8%	3%	NA

KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; SLDA, Single leaflet device attachment; RCT, randomized controlled trial; TR, tricuspid regurgitation; SD, standard deviation.

relevant. The patient population included elderly individuals (mean 78 years, 55% women), with reduced baseline QoL (mean KCCQ at baseline: 55.1 $\pm$ 23.8 points). However, only 25% of the patients were admitted for heart failure treatment in the year before enrolment, suggesting that, despite poor QoL, most TR patients remain managed in the ambulatory setting. At baseline, TR was severe or worse in almost all patients in both groups, while severe TR was still present in 95% of the control patients against 13% in the therapy arm at 1-year follow-up. This outcome contrasts with the COAPT trial, where MR was reduced significantly also in the medical arm at 2 years.¹⁰² This finding confirms the efficacy of T-TEER and underlines the inefficacy of medical therapy to control TR in symptomatic patients. The procedure was safe, with 0.6% all-cause mortality at 30 days and only a few adverse events. At 1 year, there was no difference in mortality, surgery for TR, or hospitalization rate between the two groups, while KCCQ improved by 12.3 $\pm$ 1.8 points in the TEER group, in contrast to only .6 $\pm$ 1.8 points in the control group ($P < .001$).

The improvement in QoL is similar to that observed in the device group of the COAPT trial and larger than most of the heart failure trials (Figure 6). There was a direct correlation between QoL improvement and TR reduction, suggesting a dose-effect, although a placebo effect cannot be completely excluded due to trial design (patient-reported outcome, open-label trial). The TRILUMINATE trial is a matter of intensive debate, with all its intrinsic limitations, being the randomized study of a widely undefined field of interest. While observational studies were predicting a much higher treatment impact, the TRILUMINATE trial included patients with a lower burden of symptoms (NYHA class and KCCQ) and hospitalizations before entering the study, less advanced V-STR with smaller coaptation gaps and lower incidence of left-

sided heart disease (particularly previous cardiac surgery) (Table 2). While QoL represents a relevant endpoint for elderly patients with TR, longer-term follow-up data are awaited to verify whether T-TEER can influence more objective outcomes. Unfortunately, the possibility to crossover without experiencing an event at one year by design has the potential to blunt this expectation.

Several additional randomized studies comparing different treatment strategies with conservative treatment are currently enrolling in different countries (e.g. TRISCEND II, CLASP TR, TRICI-HF in Germany and TRI-FR in France, TRICAV for heterotopic valve replacement with the TricValve system) and will provide further insights into the clinical impact of TR treatment.

Valve replacement

In the timeline of TR interventions, transcatheter tricuspid valve replacement (TTVR), as valve-in-valve¹⁰⁸ and valve-in-ring procedures, came first. The off-label implant of balloon-expandable aortic or pulmonary valves¹⁰⁹ efficiently restores failed surgical repair and replacements. The implanted prostheses function as fixation scaffold for the balloon-expandable valves. The VIVID (Valve-in-Valve International Database) registry reported outcomes of 306 patients undergoing valve-in-ring and valve-in-valve procedures, with an incidence of 17% mortality, 12% reintervention, and an 8% risk of valve-related complications at 3-year follow-up.¹¹⁰ Valve-in-ring and valve-in-valve have been performed successfully also in patients with preexisting pacemaker leads without the need for lead extraction.¹¹¹ Valve-in-ring procedures have been sometimes unsuccessful due to device and patient selection, although few reports are available in the literature.¹¹² Patient selection,

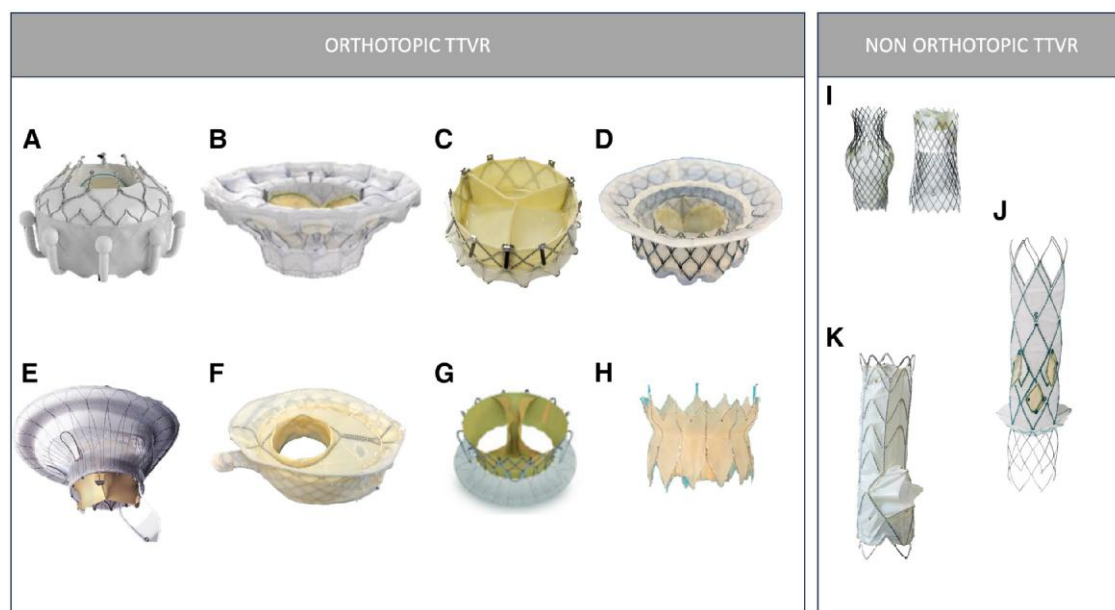


Figure 7 Transcatheter tricuspid valve replacement devices. Orthotopic devices: (A) Evoque; (B) Cardiovalve; (C) Gate; (D) Intrepid; (E) Lux valve; (F) V-Dyne; (G) Trisol; (H) Topaz Heterotopic devices; (I) Tric Valve; (J) Trillium; (K) Tricento

imaging screening, and device selection are key elements to perform a safe and simple procedure in most cases.

Balloon-expandable aortic valves have also been used as caval implants,^{113,114} although this approach has been overcome by the development of dedicated devices.

Heterotopic or caval valve implantation (CAVI) has been attempted to protect organs from venous hypertension and reduce backflow-associated TR. CAVI (Figure 7) has been mainly used in patients who either had a failed or had anatomical contraindications for a 'conventional' transcatheter intervention. However, CAVI can be performed under local anaesthesia, solely fluoro-guided and non-constrained by TV anatomy. Dedicated prostheses are available with different fixation modalities, such as single bicaval implant,¹¹⁵ or separated valves.¹¹⁶ A recent registry reported significant improvements in QoL and symptoms despite no haemodynamic improvements following CAVI.¹¹⁷ More recently, RH remodelling has been reported following CAVI, suggesting a potential prognostic value.¹¹⁸ The exact role of CAVI in the field needs to be further developed, considering its simplicity and reproducibility, with the inherent limitation of an intervention that does not address the culprit lesion.

Several orthotopic valve devices (Figure 7) are under clinical investigation, most of them derived from a mitral valve design, while few are natively for the TV. The first TTVR with a dedicated device was performed using the Gate (NaviGate Cardiac Structures, Inc.) valve.¹¹⁹ The large device, specifically designed to fit the large TV annulus, features a combination of leaflet and annular fixation. Limitations in the delivery system have confined this device to mainly direct transatrial access and have resulted in cases of malposition requiring surgical revision.

The experience with the Evoque system (Edwards Lifesciences Inc, Irvine, CA, USA), a self-expanding device using a mix of leaflet and annular fixation, with a dedicated delivery system is the largest so far. The safety-efficacy trial TRISCEND¹²⁰ collected data on 172 patients. Cardiovascular mortality was 1.7% and 9.4%, and major adverse events

were observed in 18% and 30% of patients at 30 days and 1 year, respectively. New pacemaker implantation was needed in 13% of patients within 30 days (none thereafter). At 1 year, patients had significant improvement in NYHA class, QoL, and functional status. In addition, 2 years outcomes of patients implanted under compassionate use show superimposable outcomes¹²¹ and reported a 37% increase of left ventricular forward stroke volume and improvement of hepatic function. The TRISCEND II (NCT04482062) pivotal trial comparing Evoque TTVR to medical therapy is recruiting.

Cardiovalve (Cardiovalve Inc., Or Yehuda, Israel), with leaflet fixation, requiring minimal radial force, therefore applicable to valves with large annulus, features a sealing cuff to minimize perivalvular leaks. The TARGET trial (NCT05486832) is collecting feasibility safety outcomes in an international registry. To date, more than 40 patients have been enrolled. Data from 30 compassionate-use patients report 6% mortality, 6% pacemaker implant rate, and 6% need for reintervention. At discharge, TR was less than moderate in 92% of patients (George Nickenig, PCR London Valves 2023, personal communication).

Other technologies are under investigation in an early phase, such as the Intrepid (Medtronic Inc, Minneapolis, MN, USA),¹²² the LuX-Valve¹²³ (Jenscare Biotechnology, Ningbo, China), the Vdyne (Vdyne, Minneapolis, MN, USA), the Topaz (TRiCares SAS, Paris, France) and Trisol Valve (TriSol Medical Ltd., Inc., Yokneam, Israel).

The Duo Valve (Croivalve, Dublin, Ireland) is a hybrid device implanted in the superior vena cava but acting as a coaptation device (either a valve or a spacer) at the valve level.

Spacers

Several attempts to treat atrio-ventricular valve regurgitation with spacers have been until now discouraging. These devices fill the regurgitant orifice to reduce backflow. The main limitation is the stability of fixation and efficacy in a complex 3D-shaped regurgitant orifice. The FORMA spacer was fixated at the subclavian vein and the apex of the

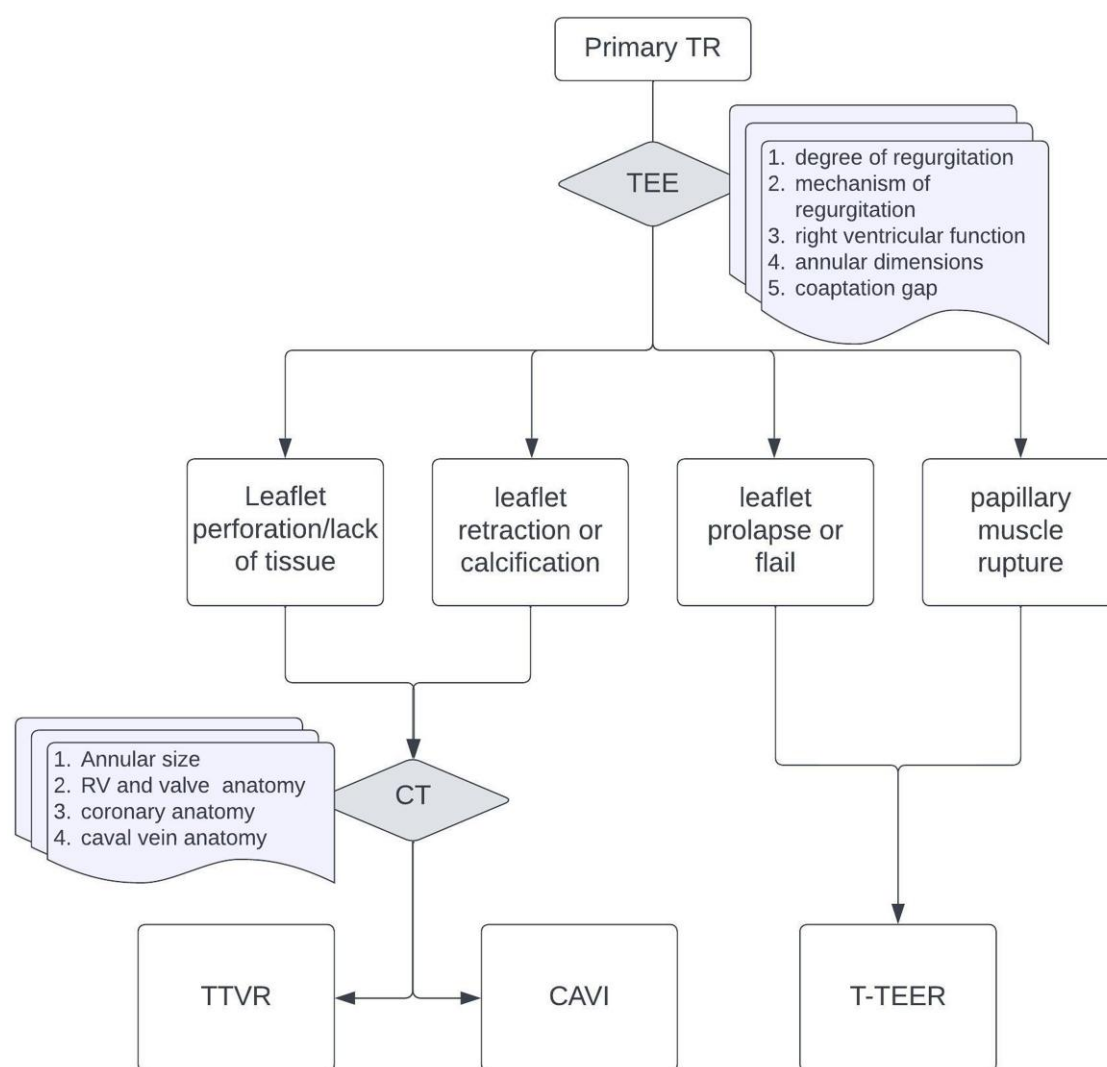


Figure 8 Decision-making and device selection algorithm for primary isolated tricuspid regurgitation. Initial echocardiographic screening, often via transoesophageal approach, is essential to evaluate the extent and cause of regurgitation and to examine right heart function and structure. If lesions are unsuitable for tricuspid transcatheter edge-to-edge repair, a cardiac computed tomography scan becomes crucial to scrutinize the anatomical details, determining suitability for alternative interventions like transcatheter tricuspid valve replacement or caval valve implantation (TEE, transoesophageal echocardiography; CT, computed tomography; TTVR, transcatheter tricuspid valve replacement; CAVI, caval valve implantation; T-TEER, tricuspid transcatheter edge-to-edge repair)

right ventricle. A multicenter registry demonstrated some reduction of regurgitation with improvement in QoL,¹²⁴ however, its production has been discontinued. A recent revival of spacers is observed,¹²⁵ regaining interest due to their independence from valve anatomy and simplicity of implant, but clinical outcomes are unavailable.^{124–126}

Device selection and screening process: tailoring the therapy to patients

Once indication for TTVI is given, based on a predicted clinical benefit in high risk or inoperable patients, TTVI device and procedure selection is a

key for success. Currently, T-TEER accounts for more than 90% of the indications. Future changes in this prevalence depend on ease of use, scalability, clinical outcomes, and availability of approved devices. Device selection is made by the Heart Team in a step-wise process that involves careful clinical and anatomical assessment. Multi-modality imaging help to assess the aetiology, mechanism of regurgitation, valve anatomy, deliverability and device eligibility, and to evaluate RV function and RH, physiology (to predict the tolerability of the procedure in end-stage patients).

In case of primary (organic) TR, T-TEER is an option for localized lesions (Figure 8). In patients with ruptured papillary muscles (usually post-traumatic), T-TEER may be considered but surgery is the most common solution.¹²⁷ Patients with restricted leaflet motion or with a lack of tissue (e.g. carcinoid disease) should be referred to TTVR

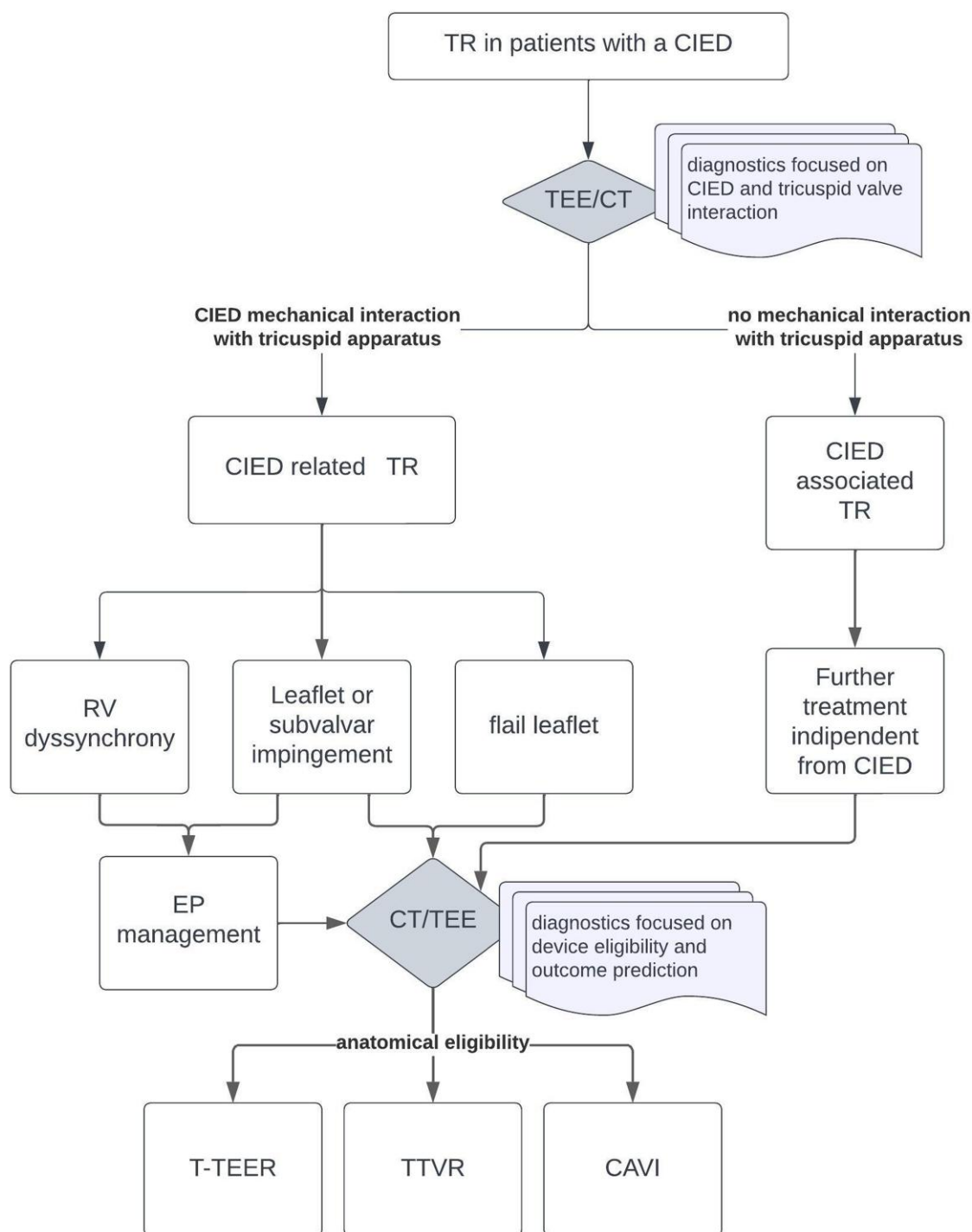


Figure 9 Decision-making and device selection algorithm for cardiac implantable electronic device-tricuspid regurgitation. Echocardiography, occasionally supplemented by CT imaging to better delineate the cardiac implantable electronic device pathway, is pivotal for evaluating how the cardiac implantable electronic device affects tricuspid valve functionality. Should the cardiac implantable electronic device be implicated in tricuspid regurgitation (cardiac implantable electronic device-related tricuspid regurgitation), interventions such as lead extraction, repositioning, or device replacement may be initiated by an electrophysiologist. Additionally, advanced imaging is indispensable for elucidating the regurgitation dynamics and for tailoring treatment to the patient's specific anatomical considerations (CIED, cardiac implantable electronic device; TEE, transoesophageal echocardiography; CT, computed tomography; EP, electrophysiology; T-TEER, tricuspid transcatheter edge-to-edge repair; TTVR, transcatheter tricuspid valve replacement; CAVI, caval valve implantation)

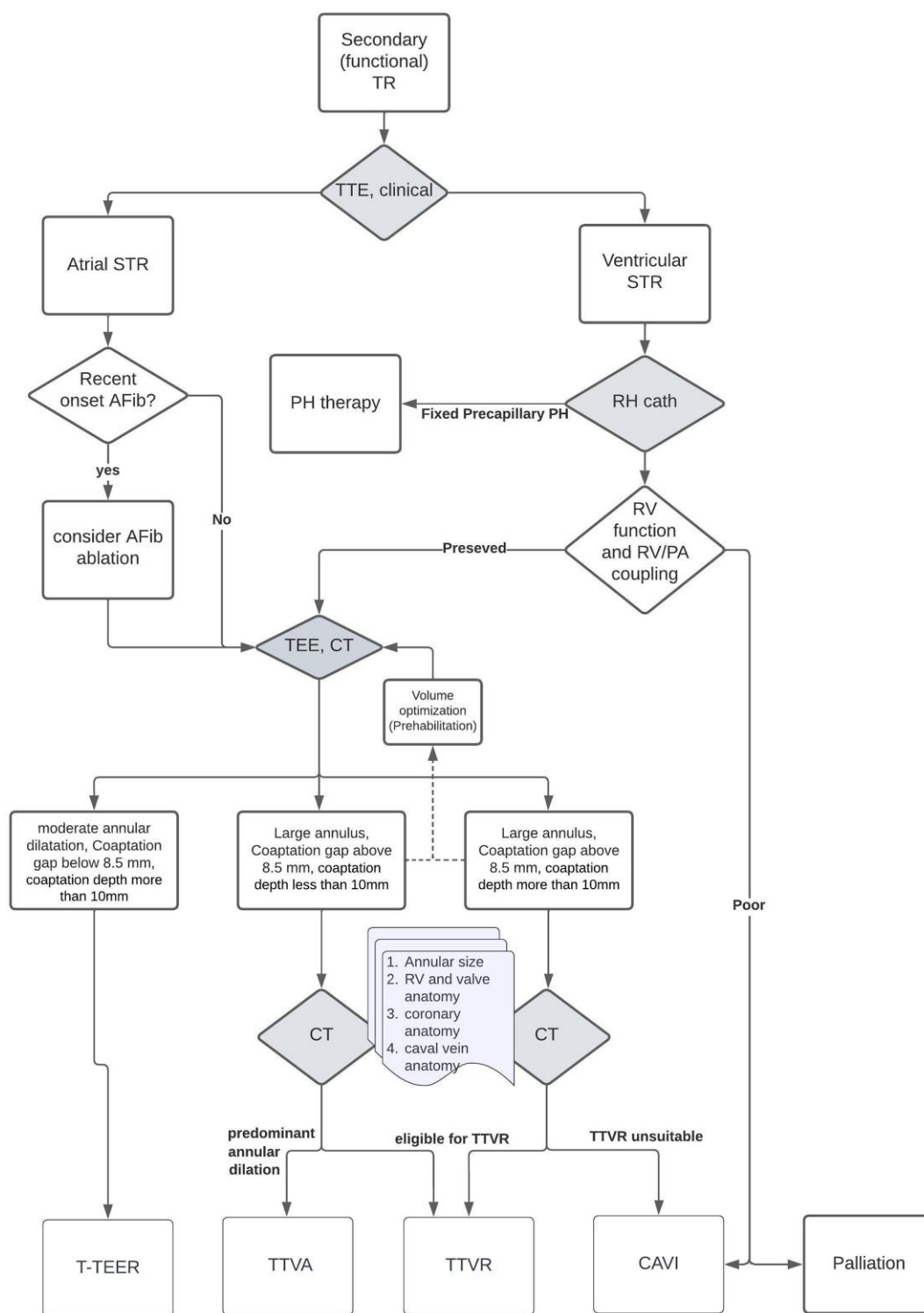


Figure 10 Decision-making and device selection algorithm for secondary isolated tricuspid regurgitation. The algorithm for decision-making in isolated secondary tricuspid regurgitation is intricate, requiring multiple steps. Initially, a distinction is made between atrial and ventricular tricuspid regurgitation based on clinical and echocardiographic data. Atrial secondary tricuspid regurgitation demands a collaborative approach with electrophysiology experts to devise rhythm management strategies. For ventricular secondary tricuspid regurgitation, especially in advanced stages, right heart catheterization is essential to gauge the severity and characteristics of pulmonary hypertension and to evaluate right heart function. The choice of intervention and device is then guided by detailed valve anatomy and cardiac function assessments through multimodal imaging (CIED, cardiac implantable electronic device; TEE, transoesophageal echocardiography; CT, computed tomography; EP, electrophysiology; T-TEER, tricuspid transcatheter edge-to-edge repair; TTVA, transcatheter tricuspid annuloplasty; TTVR, transcatheter tricuspid valve replacement; CAVI, caval valve implantation)

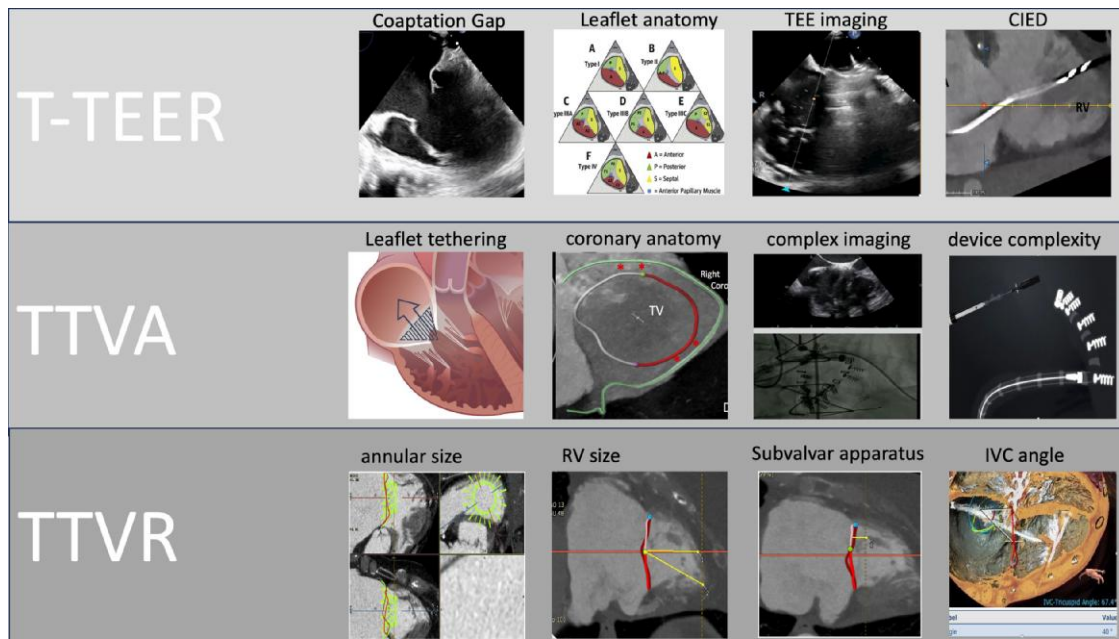


Figure 11 Device selection: key constraints of various tricuspid regurgitation treatment technologies. This figure outlines the technical obstacles for each tricuspid regurgitation treatment technology. Tricuspid transcatheter edge-to-edge repair effectiveness is constrained by factors such as the coaptation gap, leaflet number and distribution, transoesophageal echocardiography image quality, and the presence of transvalvular leads. Transcatheter tricuspid valve annuloplasty applicability is limited by the extent of right ventricular remodelling, leaflet tethering, proximity of the right coronary artery to the annulus, as well as device complexity and imaging requirements during the procedure. Transcatheter tricuspid valve replacement faces limitations due to the annulus size and shape, right ventricular dimensions, subvalvular apparatus anatomy, and the venous system's size and anatomy, with specific devices presenting unique anatomical contraindications (T-TEER, tricuspid transcatheter edge-to-edge repair; TTVA, transcatheter tricuspid valve annuloplasty; TTVR, transcatheter tricuspid valve replacement)

(when available) or CAVI. Obviously, surgery should be reconsidered in patients who are not eligible for any TTVI procedure, and is mandatory in most patients with active infective endocarditis.

Patients with CIED-related TR (Figure 9) can be challenging.¹²⁸ First, multi-modality imaging is required to determine whether TR is caused by the CIED (CIED-related TR) or the lead has no direct impact on the mechanism of regurgitation (CIED-associated TR). In very selected cases of CIED-related TR, a lead management strategy can be attempted by replacing, relocating,¹²⁹ or removing¹³⁰ the lead and implanting a valve-sparing pacemaker system (leadless pacemaker or coronary sinus lead). However, lead extraction, particularly in patients with leads entangled in the subvalvular apparatus, can worsen TR by generating additional lesions¹³¹ (even in leadless pacemakers.¹³²) In case of CIED-associated TR, T-TEER, and annuloplasty are not contraindicated and the presence of a CIED seems to have no impact on outcomes.⁷⁶ On the other hand, if the lead is actively involved and adherent to a valve structure, repair techniques should be used only in very experienced hands.

TTVR can be a good alternative, although the issue of lead management remains debated. Many patients have been treated by jailing the lead without acute effects,^{110,133} but there are some cases of damaged leads and other complex situations (e.g. need for infected lead extraction following TTVR.¹³⁴)

In the case of secondary TR (Figure 10), the treatment options are wider.²¹ Patients with A-STR can be successfully treated with either T-TEER or annuloplasty. Annuloplasty (eventually followed by TEER) can be very efficient in patients with larger coaptation gaps and minimal leaflet tethering, while T-TEER is more adequate for patients with

moderate tethering, as seen in patients with late forms of A-STR and concomitant RV remodelling.

The main limitation of T-TEER (Figure 11) is the coaptation gap and the leaflet anatomy, while annuloplasty is limited by leaflet tethering, and the anatomy of the right coronary artery. In patients with V-STR, while T-TEER remains the most common treatment, TTVR and CAVI are a potential alternative, when the right ventricle is remodelled and the disease more advanced. CAVI is an option for end-stage untreatable patients in whom a palliative approach is needed, while its use in the earlier stages is still under evaluation.¹¹⁷ Orthotopic TTVR is a very promising alternative to repair due to the predictability of TR reduction and to the ease of use. However, several anatomical limitations are excluding a large number of potential candidates. The eligibility anatomical criteria are strictly related to the delivery system and the mode of fixation of the different prostheses. They include the size and shape of the annulus, the size of the right ventricle, the quality of the leaflet tissue, and the deliverability (venous access and angle between the IVC and the valve). In addition, patients considered for TTVR undergo a more comprehensive evaluation of RV function. A suitable coupling between pulmonary resistance and RV function is considered a reliable method to exclude the risk of afterload mismatch.^{80,135–137}

Future perspectives

To optimize outcomes, awareness, and early disease detection and management have to be further encouraged. In the era of individualized precision medicine, TTVI offers the opportunity to apply innovative

treatment approaches and gain systematic evidence in a largely under-investigated field of modern cardiology. Given the high disease complexity of TR, with several clinical phenotypes and crossing patient journeys, a one-size-fits-all approach is unlikely to succeed. Novel diagnostic and patient selection tools, including artificial intelligence, able to integrate multiple variables, analyze large datasets, harmonize layers of knowledge, and competence should be implemented to guide decision-making.

Combining multi-modality imaging with circulating biomarkers may inform about the biological mechanisms that contribute to disease progression and allow for future pathway-specific therapies and personalized treatments.¹³⁸ Moreover, they may help identifying early red flags, as well as late signs of futility.¹³⁹ Further basic and clinical research is needed to identify novel biomarkers that indicate early disease of the RH.

New imaging modalities integrating augmented reality and simulation will improve training, procedural planning, and outcomes, while dedicated imaging technologies may influence the way therapies are delivered to patients. Using ICE catheter producing image quality comparable to TEE general anaesthesia may be avoided.^{50–52,140,141}

Continuous improvement of current devices and new technologies developed in a global market will also increase the treatment options and hopefully simplify the procedures. Simplicity and predictability of replacement will compete with the more physiological approach of repair. The choice depends on lifetime management perspectives with the index procedure representing only the beginning of the full patient journey.

A patient-centered approach requires therefore close collaboration between cardiology subspecialties to manage complex multimorbid patients and improve their outcomes. In an era of fragmentation and procedurally oriented medicine, a network of care dedicated to patients with RH disease integrating prevention, early diagnosis, optimal medical therapy, surgical and interventional treatments needs to come into existence.

Supplementary Data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

No data were generated or analysed for or in support of this paper.

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