CONTEMPORARY APPROACH OF TRICUSPID REGURGITATION:

KNOWNS, UNKNOWNS AND FUTURE CHALLENGES

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**ABSTRACT**

Severe tricuspid regurgitation (TR) worsens heart failure and is associated with impaired survival. In daily clinical practice, patients are referred late and tricuspid valve (TV) interventions (surgical or transcatheter) are underutilized, which leads to irreversible right ventricular (RV) damage and increases the risk. This article addresses the appropriate timing and modality for an intervention (surgical or transcatheter), and its potential benefits on clinical outcomes. Ongoing randomized controlled trials will provide further insights into the efficacy of transcatheter valve interventions compared to medical treatment.

**Keywords:** valvular heart disease; tricuspid regurgitation; transcatheter valve intervention; tricuspid valve surgery
ABBREVIATIONS

3D = three-dimensional
CIED = cardiac implantable electronic device
HF = heart failure
ICE = intracardiac echocardiography
MR = mitral regurgitation
M-TEER: mitral transcatheater edge-to-edge repair
TR = tricuspid regurgitation
T-TEER = tricuspid transcatheater edge-to-edge repair
TTVI = transcatheater tricuspid valve intervention
TTVR = transcatheater tricuspid valve replacement
TV = tricuspid valve
Epidemiology

Tricuspid regurgitation (TR) is one of the most common valvular heart diseases (VHD) after mitral regurgitation (MR). TR of any severity affects more than 65% of the general population worldwide. (1, 2) Population-based studies have suggested that clinically significant TR (moderate or higher grade) has a prevalence of 0.55% in the general population, increasing with age and reaching 6.6% in patients >75 years of age, a prevalence comparable to the one of aortic stenosis in this age category. (3, 4) Women are affected more frequently than men (5), and female sex is an independent predictor of TR severity and progression(6-8). Hypotheses to explain these sex differences include the higher prevalence of heart failure (HF) with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) in women.(9) Other clinical predictors of severity and progression of TR include older age, left ventricular dysfunction, atrial fibrillation (AF), pre- and post-capillary pulmonary hypertension(7), previous cardiac surgery(10), as well as the presence of a cardiac implantable electronic device (CIED) lead.(8)

Causes and Classification

The classification of TR has recently evolved beyond the traditional subdivision into primary and secondary disorders (Figure 1).(11-13) The current classification scheme reflects a better understanding of the various TR mechanisms and their outcomes.(14) Secondary TR is the most frequent form (more than 80%) and subdivision into an atrial and ventricular etiology has been proposed. In ventricular secondary TR, the RV is dilated (infra-annular) and the leaflets are tethered, while in atrial secondary TR a predominant annular dilation is observed and leaflet tenting is almost absent. Diagnostic parameters differentiating atrial from ventricular secondary TR have been recently proposed by the TVARC consortium and the PCR Tricuspid Focus group and are listed in Table 2(15). Secondary TR is most frequently related to left-sided VHD or left ventricular dysfunction, and pre- or post-capillary pulmonary hypertension (PHT).(3, 16, 17) In addition, cardiac implantable electronic device (CIED) lead-related TR is an increasing distinct entity that represents 10-15% of all TR and requires specific diagnostic work-up and management. (13)
About 10 to 33% of patients develop or worsen TR after implantation of a CIED RV lead (13, 18-20). Interestingly, leadless pacemaker may also impact tricuspid valve (TV) function (21), particularly when deployed into the septum close to the TV annulus (22). The diagnosis can be made non-invasively with two-dimensional (2D) transthoracic (TTE) or transoesophageal echocardiography (TEE), but further understanding of TR mechanism usually requires the use of advanced imaging techniques such as three-dimensional (3D) echocardiography(23) and/or computed tomography (CT) to establish the exact interaction between the TV and the lead(24). A prospective registry showed that TEE-guided lead implantation (pacemaker or ICD) was associated with less TR worsening compared to conventional placement.(25), although systematic implementation of echocardiographic guiding seems difficult for procedures usually performed under local anaesthesia.

Primary TR is uncommon, especially in developed countries, accounting for 5%-10% (1) of all TR and is associated with organic leaflets lesions/anomalies. Usually, primary TR is observed in Barlow’s disease, congenital heart disease (Ebstein anomaly, double-orifice TV or TV dysplasia, hypoplasia or cleft), trauma (chest wall trauma or endomyocardial biopsy), carcinoid syndrome, endomyocardial fibrosis or underlying infectious disease (endocarditis).

**Challenges of tricuspid valve imaging and treatment**

The TV apparatus anatomy is complex and its precise evaluation is key when planning TV interventions. Despite its name, the TV was found to be truly tricuspid in less than 60% of the subjects studied in a series of autopsied patients(26). This was confirmed in vivo in a multinational retrospective study analyzing TV morphologies using TEE that showed a four leaflets anatomy in 39% of the patients (Figure 2).(27)

Imaging is key to assess the TV and transcatheter procedures become extremely challenging when the transgastric short axis and the deep/mid esophageal RV inflow/outflow views are of insufficient quality.(28) The anterior location of the TV, along with right heart dilatation increase the distance between the esophagus and the right heart. Acoustic shadowing due to left-sided cardiac prostheses, lipomatosis of the interatrial septum, as well as the delivery system itself are other factors potentially limiting TEE image quality.

Four important structures are located in immediate proximity to the TV and can be damaged during TV interventions: the conduction system (atrioventricular node and right bundle of His), the right
coronary artery, the non-coronary sinus of valsalva and the coronary sinus ostium (Figure 2). Furthermore, the lack of calcium, the angulation in relation to the inferior vena cava (IVC), the anatomical variability of the subvalvular apparatus, the trabeculated and thin RV wall complicating anchoring, and the interaction with pre-existing CIED lead represent additional limitations for interventions.(29)

TR undertreatment still represents one of the main challenges and is explained by several factors. First, the misconception that TR resolves after left-sided interventions is still a prevalent opinion, even if contradicted by the available evidence. Second, TR severity is frequently underestimated, and therefore referral occurs late when irreversible RV dysfunction already increases the surgical risk. In a recent cohort study by our group, only about 10% of the patients with severe TR underwent an intervention of any kind (either surgical or transcatheter) during a follow-up period of 4 years.(30)

**Impact of TR on prognosis**

Severe TR is associated with excess mortality and morbidity. Cumulative mortality of conservatively managed severe TR is ~40%, ~50% and ~70% at 1, 2- and 4-year follow-up, respectively.(6, 30-33) This roughly corresponds to untreated symptomatic severe aortic stenosis. (34). Despite comparable prevalence and impact on clinical outcomes (2), severe TR is less frequently regarded as a factor impacting on outcomes and contributing to HF symptoms.

While TR mechanism (CIED-related, primary or secondary TR) does not appear to be a discriminant of outcomes at 5 years(35), atrial and ventricular secondary TR have a clearly distinct prognosis with lower risk of death or HF hospitalization for patients with atrial secondary TR (78% vs. 46%, log-rank chi-square: 30.759; p<0.001)(36, 37). In addition to TR aetiology, TR severity, age, severe renal failure, LV-dysfunction, PHT and RV-dysfunction all predict death in patients with severe TR.(30, 38) Recently, a machine-learning algorithm was used to classify patients with severe TR into four different “phenoclusters” with distinct outcomes in terms of death or HF hospitalization.(35) Discriminating variables were age, albumin, blood urea nitrogen, RV function, and systolic blood pressure (all p<0.05).(35) This emphasizes the fact, that beyond cardiac damages and valve anatomy, clinical factors also need to be taken into consideration when evaluating patients with severe TR.

**Severity grading and multimodality imaging**

Grading of TR severity is mainly based on the vena contracta and the effective regurgitant orifice area that was shown to continuously affect mortality with an exponential risk increase even beyond the traditional cut-off of 40mm².(39) For this reason, as well as for the purpose of device selection and result evaluation, a five-grade scheme has been proposed. (40, 41) Several cohort studies have
shown the incremental prognostic value of this 5-grade scheme with higher mortality, heart failure (HF) hospitalization, and poorer hemodynamics in patients with “massive” or “torrential” TR. (30, 42, 43) Although this classification may be useful for device selection (decision for repair versus replacement), patients should be evaluated for treatment before they reach more than severe TR.

Reproducible grading is challenging, since TR severity varies according to loading conditions and respiratory-dependent RV filling. Qualitative and semi-quantitative evaluation can be limited by the low jet velocity (or even laminar flow) that influences its visualization using Doppler echocardiography. (44) Furthermore, multiple limitations of the proximal isovelocity surface area (PISA) methodology to quantify TR should be acknowledged: the complex PISA surface (hemi-ellipsoid or even stellar rather than hemi-spherical), the high variability during the cardiac cycle, and finally the non-planar surface of the regurgitant orifice (which may require a correction for the leaflet angle). Therefore, the PISA method typically underestimates the true orifice, particularly in secondary TR by a factor close to 50%. (44) To confirm TR grading, cardiovascular magnetic resonance (CMR) should be considered since its prognostic value (regurgitant fraction >45%) has been established in patients with severe secondary TR. (45) Computed tomography (CT) has a fundamental role for the planning of transcatheter annuloplasty and replacement procedures. (44) Assessment of the tricuspid annulus dimensions and morphology, localization of the right coronary artery and its distance from the tricuspid annulus represent some of the essential informations provided by CT imaging. (46, 47)

Timing of interventions: assessment of risk and RV function

Delayed surgical treatment of patients with symptomatic severe TR contributes to the high morbidity and mortality rate observed after isolated surgical TV replacement. (48, 49) (50, 51). According to historical data including late referral and patients operated for infective endocarditis, the risk of in-hospital mortality is ~10% after isolated TV surgery. (48, 49, 52, 53) Furthermore, about two third of the patients experience at least one complication and almost 20% suffer from a major adverse event after isolated TV surgery. (48) Therefore, appropriate timing of intervention is crucial to avoid irreversible RV damage and organ failure (Table 3, Figure 3 and Figure 4). A recent single center US study including 159 patients (57.2% female) who underwent isolated tricuspid surgery between 2004 and 2018 (mean follow-up of 5.1 ± 4.0 years) compared outcomes according to the timing of surgery (115 operated when class I indication was reached, 44 operated earlier). Early surgery before reaching class I indication in patients with severe TR decreased operative mortality (0.0% vs 7.0%, p=0.107) and adverse events (18.2% vs 35.7%; p=0.036). (54)
Since usual risk scores have not been validated for TV surgery, the dedicated TRISCORE based on clinical factors has been recently proposed and was shown to outperform the STS-PROM and EuroScore/EuroScore II for the prediction of events both after isolated(55) and redo TV surgery(56). In an international multicenter registry, patients with low (≤3) and intermediate (4-5) TRISCORE derived a mortality benefit from successful TR treatment (any modalities) at 2 years, while no significant difference was found in those with higher score (≥6)(57). The MELD score initially developed to assess liver dysfunction also predicts mortality in patients undergoing TV surgery (either isolated or concomitant) and might be used as an alternative indicator of the risk of mortality.(58, 59)

In addition to scoring, comprehensive assessment of concomitant cardiac damage in patients with significant TR based on the presence of RV dysfunction and the burden of right HF symptoms, identifies candidates with worse long-term outcomes treated either conservatively(60) or surgically(61). Surgical interventions should therefore be performed early, as soon as there is evidence of RV dilatation or declining RV function.(62, 63) The recently published TVARC document(15) attempts to define cut-offs indicative of RV dysfunction severity (Table 4). While these values may provide some guidance, they should be considered with caution, since the assessment of RV function in patients with severe TR using load-dependent parameters may be unreliable and should not preclude access to a procedure.

Other parameters have been recently proposed including RV-pulmonary artery (RV-PA) coupling, which can be described as the relationship between RV contractility and RV afterload. RV contractility is a load-independent parameter(64) that is best assessed using pressure-volume loop-derived end-systolic elastance (Ees), while RV-PA coupling is assessed as a ratio of end-systolic to arterial elastances (Ees/Ea)(65). Non-invasive surrogates simplifying work-up include the tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (PASP) ratio that may help to determine whether RV function adequately responds to the existing afterload conditions(65). Recent studies showed that patients with a low TAPSE/PASP ratio (e.g. ≤0.31 or ≤0.34) had a worse prognosis than those with a higher ratio in various clinical situations, including after transcatheter TR treatment(65, 66). Nonetheless, the initial testing of this concept was conducted on patient groups without significant TR. In situations where severe TR is present, the conventional two-chamber system, comprising the RV and PA, transforms into a three-compartment system, encompassing the RV, PA, and the RA. The existence of a low-pressure outlet in the RA complicates the assessment of RV-PA coupling considerably. Furthermore, the impact of TR treatment on this three-compartment system has only been addressed in a single publication(66). RV free wall longitudinal strain (RVFLS)
has emerged as a complementary sensitive parameter for the evaluation of RV function, with the capability to detect subclinical damages that may have been missed with conventional methods.(67)
Isolated Tricuspid Valve Surgery
Early detection of TR, careful patient selection, modern surgical techniques and perioperative care have improved the prognosis of patients undergoing isolated TV surgery in recent years. Indeed, more recent data (2007-2017) from a single US tertiary center (n=95, 41% re-operations) showed a low in-hospital mortality rate of 3.2%(68). The prognostic value of timely TV surgery, particularly before the development of significant RV dysfunction, was demonstrated in a recent large retrospective study (n=534, mean age was 70.8 years, 49% male, 44% with history of previous cardiac surgery).(33) At a mean follow-up time of 38 months, patients who underwent TV surgery had better survival than those under medical treatment (62% vs 35%; p<0.001).

Isolated tricuspid valve surgery (with or without previous left-sided surgery) has a IIa indication in the latest European guidelines in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension (Table 3 and Figure 3). Tricuspid valve (TV) repair should be performed whenever possible for the treatment of TV disease requiring surgery.(62, 63) The benefit of TV repair over TV replacement has been confirmed in a recent propensity-score matched analysis (175 pairs) showing that TV repair offers lower 30-day (4.0% vs 8.0%, p = 0.115) and late mortality (cumulative survival rates at 3, 5 and 7 years: 84%, 75% and 56 % vs 71%, 66% and 58%, p=0.001) with no difference regarding reoperation rate compared with TV replacement, in particular when performed beating heart(69). Compared to suture annuloplasty (such as the De Vega annuloplasty), the implantation of a ring offers better long-term survival and freedom from recurrent TR with a trend toward fewer TV reoperations.(70) In experienced centers, most of the surgical interventions are performed nowadays from a minimally-invasive right thoracic access(71).

Tricuspid valve (TV) replacement might be required in specific situations when repair or previous replacement failed or when repair is not feasible, such as in primary TR depending on the extent and severity of the underlying pathology or in secondary TR when the TV leaflets are tethered or the annulus severely dilated.(72) Patients with pacemaker lead crossing the TV may also require valve replacement, in particular when TR is caused by the lead. A tethering height >0.5 cm and a tethering area >0.8 cm² are predictive of ≥moderate TR early and 1 year after TV annuloplasty.(73) A recent study on determinants of clinical outcomes of surgery for isolated severe TR showed that TV replacement was associated with improved survival over TV repair in the subgroup of patients with tricuspid annular diameter >44 mm.(74)

Concomitant Tricuspid Valve Surgery in Patients Undergoing left-sided Heart Surgery
According to analyses of the Society of Thoracic Surgeons (STS) National Database (2000-2010; 54’375 patients), the vast majority of TV surgeries were repairs (89%) and performed during left-
sided procedures (86%). (50) Repairs increased from 84.6% in 2000 to 89.8% in 2010 (p = 0.01). Trend analysis revealed significant changes in patient characteristics, including increasing age, higher comorbidity burden, and higher proportion of emergent cases. Several studies have challenged the notion that secondary TR may resolve once successful mitral valve surgery has been performed (75, 76).

Current guidelines recommend concomitant TV repair in patients with a dilated annulus (≥40 mm or >21 mm/m²) undergoing left-sided valve surgery, independently of TR grade (Table 3 and Figure 4). (62, 63) Concomitant annuloplasty for secondary TR results in excellent safety and survival, with freedom from moderate or worse residual/recurrent TR in 89% ± 8% at 3-year follow-up. (77) Furthermore, recent data from a randomized controlled trial suggest that TR repair is associated with a lower incidence of death, reoperation for TR, progression of TR by 2 grades from baseline, or presence of severe TR at 2 years than those who underwent mitral valve surgery alone (78). Of note, although the trial was not powered to analyze the primary endpoint (composite of reoperation for TR, progression of TR by two grades from baseline or the presence of severe TR, or death) according to the severity of TR at baseline, a post hoc analysis, showed that TR progression occurred almost exclusively in patients with moderate TR at baseline and not in those with less-than moderate TR with annular dilatation. This observation questions the recommendation to perform preventive annuloplasty in patients with a dilated tricuspid annulus and less than moderate TR. Importantly, there was a higher permanent pacemaker implantation rate in the intervention group (14.1% vs. 2.5%; rate ratio, 5.75; 95% CI, 2.27 to 14.60). (78) Observational studies have reported lower permanent pacemaker implantation rates after TV repair between 2.4% and 15%. (79-81) Interestingly, in a recent nationwide (n=1502) study performed between 2006 to 2020 in Sweden, a similar 30-day permanent pacemaker implantation rate (14.2%) was observed. (82) Independent risk factors were concomitant mitral valve surgery (odds ratio, 2.07; 95% CI, 1.34-3.27), ablation surgery (odds ratio, 1.59; 95% CI, 1.12-2.23), and surgery performed in a low-volume center (odds ratio, 1.85; 95% CI, 1.17-2.83). (82) However, permanent pacemaker implantation did not increase long-term mortality, or the cumulative incidence of HF and major adverse cardiovascular events, but was associated with several short- and long-term complications such as thrombosis, infection, pacemaker-induced TR, and pacing-induced ventricular dysfunction. (83)

**Transcatheter Interventions for Tricuspid Regurgitation**

Tricuspid transcatheter interventions emerge as attractive alternatives to open-heart surgery. A IIb recommendation for transcatheter therapies in inoperable patients with secondary TR has been first introduced in the 2021 ESC/EACTS European Valvular Heart Disease Guidelines (Table 3) based on a
propensity-matched cohort study (213 pairs) suggesting that the prognosis of patients with severe TR is improved after transcatheter compared to conservative treatment(31).

Tricuspid transcatheter edge-to-edge repair (T-TEER) is the most frequently used technique(84-86) and the first-line option in patients with primary TR by flail/prolapse, and in patients with secondary TR with a coaptation gap <8.5mm, an antero-septal jet location and mild/moderate tethering (Figure 5).(11) In addition to a growing corpus of observational data supporting the procedure, the recently published TRILUMINATE trial was the first randomized prospective multicenter study to compare interventional TR management to medical treatment. The primary endpoint was a hierarchical composite that included death from any cause or TV surgery; HF hospitalization; and an improvement in quality of life as measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ), with an improvement defined as an increase ≥ 15 points in the KCCQ score at 1 year. Superiority was met for T-TEER (win ratio, 1.48; 95% CI, 1.06-2.13; P=0.02), but was driven by quality of life improvement only. While no significant differences were found regarding 6-minute walking distance (6MWD) in the initial cohort, statistical significance was reached (paired difference 27m; p=0.01) in the recently presented extended cohort (n=572). Although patients were not blinded due to the nature of the study, and a placebo effect cannot be ruled out, almost twice as many patients in the T-TEER group had an improvement of ≥15 points, and its magnitude was closely related to TR reduction. In addition, the procedure was extremely safe and the result sustained at 1 year(87). Compared to real world registries (PASTE, bRIGHT, TRISCEND I), the participants in the TRILUMINATE trial had less HF events and symptoms before inclusion, a smaller coaptation gap and a lower pacemaker rate and may therefore represent a less advanced and complex population in whom early mortality reduction is rather unlikely to be observed. Several other randomized trials are ongoing in different countries and may provide further information on the best candidates, as well as the most appropriate timing of intervention.

In analogy to surgical repair, transcatheter annuloplasty may be particularly advantageous for patients with predominant annular dilatation (in particular atrial secondary TR) with central jet location, and without extensive coaptation gap, pseudoprolapse or severe leaflet tethering (Figure 5),(11) Transcatheter annuloplasty mimic surgical repair techniques and counteract one of the main mechanism of secondary TR by directly reducing the annular dimensions. The Cardioband tricuspid direct annuloplasty system is the only one approved in Europe. In the multicentre, prospective TRI-REPAIR study, the septolateral annular diameter was reduced by 16% (p=0.006, paired analysis compared to baseline) and 72% of the patients (p=0.016, paired analysis compared to baseline) had ≤moderate TR grade and more than 80% of the patients remained NYHA Class I/II at 2-year follow-up.(88) Importantly, the efficacy and safety of the procedure were not affected by leaflet
morphology, including complex anatomies with > 3 leaflets. Limitations include procedure complexity and duration, the risk of damaging the right coronary artery and poor effect in patients with large anatomy and severe leaflet tethering. In patients with advanced TR with extensive coaptation gap and more than moderate leaflet tenting, annuloplasty alone may not be sufficient. A staged approach including annuloplasty with subsequent T-TEER may represent a valuable option in well informed candidates accepting the perspective of two separate procedures (Figure 5).

For patients with an anatomy unsuitable for repair, transcatheter tricuspid valve replacement (TTVR) emerges as the most appropriate option (Figure 5). The one-year results of the single-arm, prospective, global, multicenter TRISCEND study of the EVOQUE TTVR system showed excellent efficacy and quality-of-life improvement in symptomatic patients suffering from ≥moderate secondary or primary TR. At 1-year, 90.1% survival and 88.4% freedom from HF hospitalization were reported, while 97.6% of patients had mild or trace TR and 93% were NYHA class I or II with significant improvement in quality of life. Adverse events consisted of permanent pacemaker implantation in 13% of the patients within 30 days and the occurrence of severe bleedings in about one fourth of the patients due to the necessity of oral anticoagulation after the procedure. Six-month results from the randomized TRISCEND II study were recently presented and confirmed the risk of adverse events compared to medical treatment alone, while showing a promising effect on quality of life metrics (ΔKCCQ 17.8 points; Δ6MWD 30.9m) that could potentially translate into a reduction of hard clinical endpoints during continuous patient follow-up. Table 5 summarizes the advantages and disadvantages of transcatheter TV repair and replacement, as well as potential criteria favoring replacement. Particular care is required when considering lead jailing during TTVR since lead dysfunction can infrequently occur. Systematic device interrogation before the planning of the intervention to evaluate the consequence of a potential lead malfunction during the procedure and involvement of electrophysiologists are of paramount importance.

Heterotopic caval valve implantation may be considered after exclusion of the feasibility of repairing or replacing the TV. Heterotopic caval valve implantation (nowadays usually bicaval) aims to mitigate symptoms related to TR and associated RV failure, reduce venous congestion and limit renal and hepatic damage. Dedicated bicaval systems (Tricento, TricValve, and Trilium) are emerging and the early clinical experience shows promising results with signs of RV reverse remodeling and improvement in both quality of life metrics and NYHA functional class up to 6-month follow-up.
Combined transcatheter treatment of mitral and tricuspid regurgitation

The concept that TR does not resolve after successful treatment of MV disease keeps true for high risk patients undergoing transcatheter treatment. In patients undergoing mitral TEER (M-TEER), a retrospective study suggested that the degree of TR remained unchanged or worsened in almost 80% of patients at 1 year follow-up after M-TEER (94), while another study reported that 70% of patients with more than moderate TR before M-TEER still had relevant TR after 2 years of follow-up (95). In patients with combined MR and TR at increased surgical risk, recent hypothesis-generating data suggest that combined mitral and tricuspid TEER may be associated with improved 1-year survival compared with isolated M-TEER (96). Data from the TriValve and TRAMI registries indicate that combined M-TEER and T-TEER provide superior hemodynamic and functional outcomes (NYHA functional class, NT-proBNP levels, and 6MWD) compared with isolated M-TEER, and are associated with reduced rates of HF hospitalizations up to 18 months of follow-up (84).

Concomitant transcatheter treatment of TR during non-tricuspid interventions aims to replicate the surgical approach. However, the advantage of transcatheter treatment is the possibility to stage the procedures and therefore follow the evolution of TR after successful correction of left-sided disease. The timing of each intervention can be optimized to avoid unnecessary procedures and the approach adapted to disease etiology (e.g. atrial versus ventricular secondary TR, the presence and type of PHT and the presence or absence of RV-PA uncoupling)(97). Prospective data are needed to evaluate different strategies and the most appropriate timing of the second valve procedure.

Postinterventional care and follow-up

Since most TR patients (~70%) suffer from atrial fibrillation (AF)(30, 33), oral anticoagulation (OAC) with vitamin-K antagonist or direct oral anticoagulant (DOAC) are indicated in the vast majority of TR patients.

For those in sinus rhythm after surgical or transcatheter TV repair (T-TEER or transcatheter tricuspid annuloplasty) single antiplatelet therapy with aspirin for up to 6 months should be considered.(98)

After valve replacement a strict anti-thrombotic regimen should be observed, since the thrombotic risk is higher in the low-pressure right heart system, particularly in the early post-interventional phase and hypoattenuated leaflet thickening has been described after TTVR (99). However, the current evidence does not support any specific antithrombotic regimens. DOAC and VKA preferably long-term have been both used in ongoing studies investigating transcatheter replacement systems .(98) The combination with aspirin has also been suggested in selected cases, in particular after the detection of hypoattenuated leaflet thickening, but certainly carries a relevantly higher bleeding risk.
In patients with HF with reduced ejection fraction (HFrEF), HF therapy should be maintained according to guidelines (100), and may even be uptitrated after improvement in renal function as a result of improved cardiac output, reduced venous congestion and better renal perfusion. In patients with HF with mildly reduced ejection fraction (HFmrEF) or HfPEF, which are prevalent among patients with TR,(101, 102) SGLT2 inhibitor treatment should be maintained due to its diuretic, nephro-protective, and symptomatic effects.(103, 104) In case of residual TR, to counterbalance the activation of the renin-angiotensin-aldosterone system associated with hepatic congestion, an aldosterone antagonist may be considered under regular monitoring of renal function and electrolytes. Finally, to allow reverse remodeling of the RV, patients should maintain the pre-procedural diuretic regimen for at least 3 months after TTVI. Few patients may require careful down-titration of diuretics if they experience early post-procedural polyuria (usually within 24-48 hours) due to increased renal arteriovenous pressure gradient.

To prevent infective endocarditis, all patients with corrected TR should receive lifelong antibiotic prophylaxis due to the increased risk of bacteraemia in the venous circulation.

Post-procedure, outpatient follow-ups are usually recommended at 1, 6, and 12 months, followed by annual visits. These assessments should include monitoring of NT-proBNP, renal and liver function, TTE, and NYHA class and quality of life assessment.

**Future perspectives and challenges: the essential role of imaging**

Several unknowns remain concerning the impact of surgical or transcatheter TR treatment on hard clinical endpoints, especially hospitalization for HF and mortality (Figure 6). In addition, the exact timing of intervention in relation with the occurrence of progressive cardiac damage, as well as clinical disease progression with renal and liver impairment have to be defined.

In patients undergoing TTVR, the appropriate antithrombotic treatment balancing the risk of bleeding with those of thrombotic leaflet thickening and valve thrombosis also require further investigations.

Imaging for diagnosis and procedural guiding remain one of the most important limitation of TTVI. Parameters for accurate and reproducible assessment of the RV in patients with severe TR (ideally preload independent) still need to be defined and prospectively investigated.

While TEE remains the standard for transcatheter TV procedures, 3D intra-cardiac echocardiography (ICE) plays an emerging role, either as an adjunctive or standalone tool in patients with contraindications to TEE or insufficient imaging quality. (105, 106) Theoretically, ICE does not require
general anesthesia, which is particularly attractive for elderly or polymorbid patients. (105, 107) Latest ICE catheters (Table 6) provide 3D images with the possibility to image the cardiac structures in two or several planes simultaneously using either X-plane (Philips) or multiplanar reconstruction, which is essential for all techniques relying on leaflet grasping for anchoring (Figure 7). Current downsides include limited resolution for 3D images, interactions with the delivery catheter impairing stability, and an imaging resolution inferior to TEE, in particular in patients with a severely enlarged right atrium. The adjunction of a steerable sheath is able to improve imaging stability, but further increases costs. Since the catheter is introduced via the femoral venous access, French size is of less relevance.

Fusion imaging between TEE and fluoroscopy represent another innovative imaging technique improving orientation in the right heart chambers (Figure 7). Although a detailed visualization of the anatomy is not possible, the superimposed model based on automatic structure recognition using the echocardiographic images contribute to optimize catheter trajectory and device orientation.

Conclusions
The intensive research activities around the TV and the right side of the heart during recent years have dramatically changed the perception of TR as a clinical entity and an important contributor to the burden of HF. Technological evolution of imaging and interventions, as well as improved surgical outcomes in well-selected patients offer novel treatment opportunities. Although the impact of TR treatment on hard endpoints still need to be demonstrated irrespective of the technique, relevant quality of life improvement depending on the magnitude of TR correction has been confirmed by two recent randomized trials. Further research is needed to understand which patients of this extremely heterogeneous population benefit the most from an intervention performed at an expert center.

**FIGURES LEGENDS**

**Figure 1:** Novel classification of TR based on disease mechanism
HFpEF = heart failure with preserved ejection fraction. CIED = cardiac implantable electronic device. PM = pacemaker. RA = right atrium. RV = right ventricle.

**Figure 2:** Challenges of TV assessment and treatment.
AV = atrioventricular. RCA = right coronary artery. TEE = transesophageal echocardiography. TV = tricuspid valve
Adapted from Hahn RT et al. JACC CV imaging 2021. Proposal for a Standard Echocardiographic Tricuspid Valve Nomenclature(27).

The X-axis represents the dedicated step-by-step work-up of a patient with TR, while the Y-axis highlights the increasing degree of complexity when challenges (complex anatomy, imaging quality, surrounding structures, procedural challenges) are accumulating.

**Figure 3:** Algorithm for tricuspid valve treatment in patients without concomitant left-sided valve disease.

CIED = cardiac implantable electronic device. LV = left ventricle (left ventricular). PHT = pulmonary hypertension. RV = right ventricle (right ventricular). TR = tricuspid regurgitation. TV = tricuspid valve.

Adapted from ESC/EACTS Guidelines for the management of valvular heart disease(62) and Praz F. et al. Transcatheter treatment for tricuspid valve disease. Eurointervention, 2021 (11)

**Figure 4:** Algorithm for tricuspid valve treatment in patients with concomitant left-sided valve disease.

CIED = cardiac implantable electronic device. TA = tricuspid annulus. TR = tricuspid regurgitation. TV = tricuspid valve.

Adapted from ESC/EACTS Guidelines for the management of valvular heart disease(62) and Praz F. et al. Transcatheter treatment for tricuspid valve disease. Eurointervention, 2021 (11)

**Figure 5:** Algorithm for transcatheter tricuspid valve treatment in patients at increased surgical risk

CIED = cardiac implantable electronic device. TR = tricuspid regurgitation. T-TEER = tricuspid transcatheter edge-to-edge repair. TTVR = transcatheter tricuspid valve replacement.

Adapted from ESC/EACTS Guidelines for the management of valvular heart disease(62) and Praz F. et al. Transcatheter treatment for tricuspid valve disease. Eurointervention, 2021 (11)

**Figure 6:** Future prospects and challenges of tricuspid valve interventions

RV = right ventricle. TR = tricuspid regurgitation

**Figure 7:** Imaging innovations for the guiding of transcatheter tricuspid valve procedures

Panel A: Fluoroscopy view of the ICE catheter position relative to the T-TEER delivery catheter in the right atrium; Panel B: multiplanar reconstruction provided by the newest Siemens LUMOS 4D ICE system during mainly ICE-guided T-TEER in a patient with TEE imaging quality; Panel C: Fusion imaging between fluoroscopy and TEE (latest version of the Philips EchoNavigator) during transcatheter tricuspid valve replacement with the Edwards EVOQUE system; Panel D: Simultaneous multiplanar reconstruction allowing controlled valve deployment in all 3 dimensions.

ICE = intracardiac echocardiography. TEE = transesophageal echocardiography
AUTHORS CONTRIBUTIONS

DS and FP wrote most of the manuscript. CD, NB and DR revised the article for important intellectual content.

FUNDING/SUPPORT

None.

PATIENT CONSENT STATEMENTS

The authors confirm that patient consent is not applicable to this article, as it is a review article.

CONFLICT OF INTEREST

DS received funding for an online course from Edwards Lifesciences. FP was compensated for travel expenses by Abbott Vascular, Edwards Lifesciences, Polares Medical, Medira, and Siemens Healthineers.
REFERENCES


91. one-year data on transfemoral transcatheter tricuspid valve replacement [press release]. 2022.
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<th>Etiology</th>
<th>Pathophysiology and Morphology</th>
</tr>
</thead>
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<tr>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Rheumatic</td>
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<th>Pathophysiology and Morphology</th>
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<td>RA: severely dilated</td>
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<td>HFpEF</td>
<td>Annulus: dilated</td>
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<tr>
<td></td>
<td></td>
<td>RV: normal/dilated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leaflets: normal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ventricular secondary TR</th>
<th>Etiology</th>
<th>Pathophysiology and Morphology</th>
</tr>
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<td>Pulmonary hypertension (pre-capillary or post-capillary)</td>
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<td></td>
<td>Primary RV dysfunction</td>
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<td></td>
<td></td>
<td>RV: significant dilatation/dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leaflets: morphology normal/tethering</td>
</tr>
</tbody>
</table>
HFpEF = heart failure with preserved ejection fraction. CIED = cardiac implantable electronic device. PM = pacemaker. RA = right atrium. RV = right ventricle.

**Table 2:** Proposed main criteria for the diagnosis of atrial and ventricular secondary TR

<table>
<thead>
<tr>
<th>Leaflet Morphology</th>
<th>A-STR Phenotype</th>
<th>V-STR Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenting height (4Ch mm)</td>
<td>≤9</td>
<td>&gt;9</td>
</tr>
<tr>
<td>Right Heart Chamber Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV midventricular diameter, mm</td>
<td>≤38</td>
<td>&gt;38</td>
</tr>
<tr>
<td>End-systolic RA:RV area ratio</td>
<td>≥1.5</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>Right Ventricular Systolic Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>&gt;17</td>
<td>≤17</td>
</tr>
<tr>
<td>FAC (%)</td>
<td>≥35</td>
<td>&lt;35</td>
</tr>
<tr>
<td>RVFWFS (%)</td>
<td>≥20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>RV TDI S’ (cm/s)</td>
<td>≥9</td>
<td>&lt;9</td>
</tr>
<tr>
<td>3D RVEF (%)</td>
<td>≥50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>LVEF</td>
<td>≥50</td>
<td>Variable</td>
</tr>
</tbody>
</table>

| Invasive Pulmonary Vascular hemodynamics         |                 |                 |
| PCWP, mmHg                                       | ≤15             | Variable        |
| mPAP, mmHg                                       | <20             | Usually >20     |
| PVR (Woods Units)                                | <2.0            | Variable        |

Adapted from TVARC/PCR Tricuspid Focus Group criteria (15). 2D = two-dimensional, 3D = three-dimensional, 4Ch = four chamber view, A-STR = atrial secondary tricuspid regurgitation, EF = ejection fraction, LV = left ventricular, RV = right ventricular, V-STR = ventricular secondary tricuspid regurgitation, WU = Woods Units
Table 3: American and European Guidelines on the surgical and transcatheater management of tricuspid regurgitation.

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Level of evidence and class of recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AHA/ACC (2020)</td>
<td>ESC/EACTS (2021)</td>
</tr>
<tr>
<td><strong>Primary TR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe primary TR undergoing left-sided valve surgery</td>
<td>I-B</td>
<td>I-C</td>
</tr>
<tr>
<td>Symptomatic severe isolated primary TR without severe RV dysfunction</td>
<td>Ila-B</td>
<td>I-C</td>
</tr>
<tr>
<td>Moderate (Progressive) primary TR undergoing left-sided valve surgery</td>
<td>Ila-B</td>
<td>Ila-C</td>
</tr>
<tr>
<td>Asymptomatic severe isolated TR and progressive RV dilatation or dysfunction</td>
<td>IIb-C</td>
<td>Ila-C</td>
</tr>
<tr>
<td><strong>Secondary TR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe secondary TR undergoing left-sided valve surgery</td>
<td>I-B</td>
<td>I-B</td>
</tr>
<tr>
<td>Mild or moderate (Progressive) secondary TR with dilated annulus (≥40mm or &gt;21mm/m²) undergoing left-sided valve surgery</td>
<td>Ila-B</td>
<td>Ila-B</td>
</tr>
<tr>
<td>Mild or moderate (Progressive) secondary TR undergoing left-sided valve surgery even in the absence of annular dilatation when previous right HF has been documented</td>
<td>Ila-B</td>
<td>-</td>
</tr>
<tr>
<td>Severe secondary TR (with or without previous left-sided surgery) who are symptomatic or have RV dilatation, in the absence of severe RV or LV dysfunction and severe</td>
<td>-</td>
<td>Ila-B</td>
</tr>
<tr>
<td>pulmonary vascular disease/hypertension</td>
<td>Symptomatic severe isolated secondary TR attributable to annular dilation (in the absence of PHT or left-sided disease) who are poorly responsive to medical therapy</td>
<td>IIa-B</td>
</tr>
<tr>
<td>Symptomatic severe secondary TR after previous left-sided surgery and in the absence of recurrent left-sided valve dysfunction, surgery may be considered in the absence of severe RV dysfunction or severe pulmonary hypertension</td>
<td>IIb-B</td>
<td>-</td>
</tr>
<tr>
<td>Transcatheter treatment of symptomatic secondary severe tricuspid regurgitation may be considered in inoperable patients at a Heart Valve Centre with expertise in the treatment of tricuspid valve disease.</td>
<td>-</td>
<td>IIb-C</td>
</tr>
</tbody>
</table>

**CIED-related TR**

| No recommendation | No recommendation |

Adapted from 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease(63) and 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease(62)
Table 4: Proposed Echocardiographic Cutoffs for Right Ventricular Function according to TVARC

<table>
<thead>
<tr>
<th></th>
<th>Mild Dysfunction</th>
<th>Moderate Dysfunction</th>
<th>Severe Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAPSE, mm</td>
<td>14-17</td>
<td>10-13</td>
<td>&lt;10</td>
</tr>
<tr>
<td>RV TDIs', cm/s</td>
<td>9-11</td>
<td>6-8</td>
<td>&lt;6</td>
</tr>
<tr>
<td>RV GLS,</td>
<td>%</td>
<td>a</td>
<td>18-21</td>
</tr>
<tr>
<td>RV FWS,</td>
<td>%</td>
<td>a</td>
<td>20-23</td>
</tr>
<tr>
<td>FAC, %b</td>
<td>34-37</td>
<td>30-33</td>
<td>&lt;30</td>
</tr>
<tr>
<td>RVEF (3DE), %</td>
<td>45-50</td>
<td>35-45</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>

Table 5: Advantages and disadvantages of transcatheter TV repair and replacement (with anatomical criteria favoring replacement)

<table>
<thead>
<tr>
<th>Transcatheter valve repair</th>
<th>Transcatheter valve replacement</th>
<th>Criteria favouring orthotopic TV replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>High procedural safety</td>
<td>Higher risk of complications</td>
<td>Large coaptation gap and predominantly central gap</td>
</tr>
<tr>
<td>Minimal interaction with the native anatomy</td>
<td>Risk of new pacemaker implantation Interaction with the subvalvular apparatus or RV lead</td>
<td>Severe leaflet tethering Incidental or interacting CIED RV lead Complex leaflet</td>
</tr>
</tbody>
</table>
Low thrombogenicity

Risk of valve thrombosis

morphology (>3)

Leaflet thickening/perforation shortening (rheumatic, carcinoid, postendocarditis)

Previous surgical repair or bioprosthetic valve replacement

Reduction of regurgitation

Highly effective in reducing regurgitation

Risk of hemolysis associated with PVL

Durability likely (though unknown)

Higher risk of recurrent TR during long-term FU

Adapted from Praz F. et al. Transcatheter treatment for tricuspid valve disease. Eurointervention, 2021(11)

CIED: cardiac implantable electronic device; FU: follow-up; PVL: paravalvular leak; RV: right ventricular; TV: tricuspid valve.

**Table 6:** Currently available intracardiac echocardiography (ICE) catheters and their characteristics

<table>
<thead>
<tr>
<th></th>
<th>BioSense Webster</th>
<th>Siemens</th>
<th>Philips</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compatible Console</strong></td>
<td>GE</td>
<td>Siemens</td>
<td>Philips EPIQ</td>
</tr>
<tr>
<td><strong>Product Name</strong></td>
<td>NuVision</td>
<td>AcuNav Volume</td>
<td>VeriSight Pro</td>
</tr>
<tr>
<td><strong>Catheter size</strong></td>
<td>10F</td>
<td>12.5F</td>
<td>9F</td>
</tr>
<tr>
<td><strong>Transducer element</strong></td>
<td>Array/840</td>
<td>Twisted linear/128</td>
<td>xMatrix/840</td>
</tr>
<tr>
<td><strong>Sector Size</strong></td>
<td>90X90</td>
<td>90X50</td>
<td>90X90</td>
</tr>
<tr>
<td><strong>Working Length</strong></td>
<td>90cm</td>
<td>90cm</td>
<td>90cm</td>
</tr>
<tr>
<td>Feature</td>
<td>Site 1</td>
<td>Site 2</td>
<td>Site 3</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>2D and 3D Imaging</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3D Color Imaging</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Live X Plane Imaging</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MultiVue/MultiPlanar</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reconstruction</td>
<td></td>
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# Etiology

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<tr>
<th><strong>CIED-related TR (10-15%)</strong></th>
<th></th>
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<tbody>
<tr>
<td>CIED RV leads</td>
<td>RA: normal/dilated</td>
</tr>
<tr>
<td>Leadless cardiac pacemaker</td>
<td>Annulus: normal/dilated</td>
</tr>
<tr>
<td></td>
<td>RV: normal/dilated in particular in patients with permanent RV pacing</td>
</tr>
<tr>
<td></td>
<td>Leaflets: impingement, chordal rupture, adherence, laceration, perforation</td>
</tr>
</tbody>
</table>
Level of difficulty

Treatment

Assessment

Complex tricuspid valve anatomy

Imaging quality

Surrounding structures

Procedural challenges

- Incidence of Tricuspid Morphologies
- RCA
- Anteroseptal commissure
- Membranous septum
- AV node
- Coronary sinus
- Postero septal leaflet
- Anterior leaflet
- Posterior leaflet

- Type I
- Type II
- Type IIA
- Type IIB
- Type IIC
- Type IV

A = Anterior
P = Posterior
S = Septal
- Anterior Papillary Muscle
Tricuspid regurgitation (TR) without concomitant left-sided valve disease

Severity/aetiology of TR

Severe secondary TR

Severe RV/LV dysfunction or severe PHT

Yes

No

Severe CIED-related TR

Consider lead revision/removal

Persistent TR

Symptomatic

RV dilatation or annular dilatation

Appropriate for surgery according to the Heart Team

Yes

Yes

No

Late presentation or advanced disease

RV dilatation or annular dilatation

No

Yes

Medical therapy

Evaluation of heterotopic transcatheter TV replacement

Symptomatic

Yes

No

Evaluation of transcatheter TV therapy

Tricuspid valve (TV) surgery (repair rather than replacement when possible)

Symptomatic

Yes

No

Tricuspid Valve Regurgitation Without Left-Sided Valve Disease
Tricuspid regurgitation (TR) with indication for left-sided valve surgery recommended by the Heart Team

Severity/aetiology of TR

- Non-severe TR and TA dilatation
  - No
  - Yes

- Moderate (progressive) primary TR
  - Yes

- Severe primary or secondary TR
  - Yes

- Severe CIED-related TR
  - Yes
  - Can perioperative removal/repositioning be performed with good results?
    - Yes
    - No

No concomitant TV surgery

TV surgery (repair should be preferred to replacement)

≥ mild TR with previous right heart failure

≥ mild TR with previous right heart failure

No concomitant TV surgery

TV surgery (repair should be preferred to replacement)
Tricuspid regurgitation (TR) and high risk for valve surgery according to the Heart Team

Severity/aetiology of TR

Severe secondary TR

Severe CIED-related TR

Consider repositioning/removal/leadless device/coronary sinus lead

Persistent TR

Small coaptation gap
Central jet location
Mild tethering

Extensive coaptation gap
Moderate/severe tethering

Small coaptation gap
Commissural jet location
Mild/moderate tethering

Prolapse/Flail

Leaflet restriction/perforation
(Hedinger Syndrom, rheumatic, post-endocarditis)

Late presentation or advanced disease

Medical therapy
Evaluating heterotopic transcatheter TV replacement

Annuloplasty
T-TEER

Orthotopic TTVR (Annuloplasty ± T-TEER)

T-TEER

Orthotopic TTVR