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Review Article

Tricuspid valve regurgitation: current diagnosis and treatment

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Abstract: Tricuspid regurgitation (TR) is present in 1.6 million individuals in the United States and 3.0 million people in Europe. Functional TR, the most common form of TR, is caused by cardiomyopathies, LV valve disease, or pulmonary disease. The five-year survival with severe TR and HFrEF is 34%. Echocardiography can assess the TR etiology/severity, measure RA and RV size and function, estimate pulmonary pressure, and characterize LV disease. Management includes diuretics, ACE inhibitors, and aldosterone antagonists. Surgical annuloplasty or valve replacement should be considered in patients with progressive RV dilatation without severe LV dysfunction and pulmonary hypertension. Transcatheter repair/replacement is possible in patients with a LVEF <40%, dilated annuli, and impaired RV function. The diagnosis and treatment of TR, including coaptation, annuloplasty devices and prosthetic valves, success rates, morbidity/mortality, and trials are discussed. Transcatheter tricuspid valve repair/replacement is an emerging therapy for high-risk patients with TR who would otherwise have a dismal clinical prognosis.

Keywords: Tricuspid valve anatomy, primary tricuspid regurgitation, functional tricuspid regurgitation, tricuspid valve surgery, transcatheter tricuspid valve repair

Introduction

Clinically relevant tricuspid regurgitation (TR) is present in approximately 1.6 million individuals in the United States, 3.0 million individuals in Europe, and in more than 70 million people worldwide [1, 2]. Functional TR is the most common form of TR and is due to dilation of the tricuspid valve (TV) annulus from RV (Right Ventricle) or right atrial remodeling. The most common etiologies for functional TR are left heart failure, aortic or mitral valve disease, or pulmonary disorders with pulmonary hypertension [3]. Women are 4.3 times more likely to be affected with TR than men [3].

In the past, the function of the tricuspid valve has been considered by the medical community to be significantly less important than the function of the aortic and mitral valves. Moreover, severe TR was previously thought to be well tolerated by patients who were treated with medical management. The current thinking about the tricuspid valve has significantly changed. Mild or moderate degrees of functional TR, if uncorrected during left-sided heart valve surgery, can progress in ≥25% of patients and result in right heart failure, increased hospitalizations for heart failure, and decreased survival over four years regardless of the left ventricle (LV) ejection fraction, right ventricle (RV) size, or pulmonary artery pressure [2, 4-6]. As a consequence, cardiothoracic surgeons and interventional cardiologists have begun focusing on tricuspid valve (TV) repair or replacement. This review discusses the TV anatomy, the pathological changes that can occur in TV, the non-invasive imaging techniques available for quantification of TV disease severity, the surgical and transcatheter procedures available for TV repair or replacement, and the associated clinical trials so that physicians can properly treat patients with TR who otherwise would have a dismal clinical prognosis.

Anatomy

The TV is the largest and the most apically positioned of the four valves in the heart and has a normal orifice area of 7 to 9 cm^2 [7]. The normal

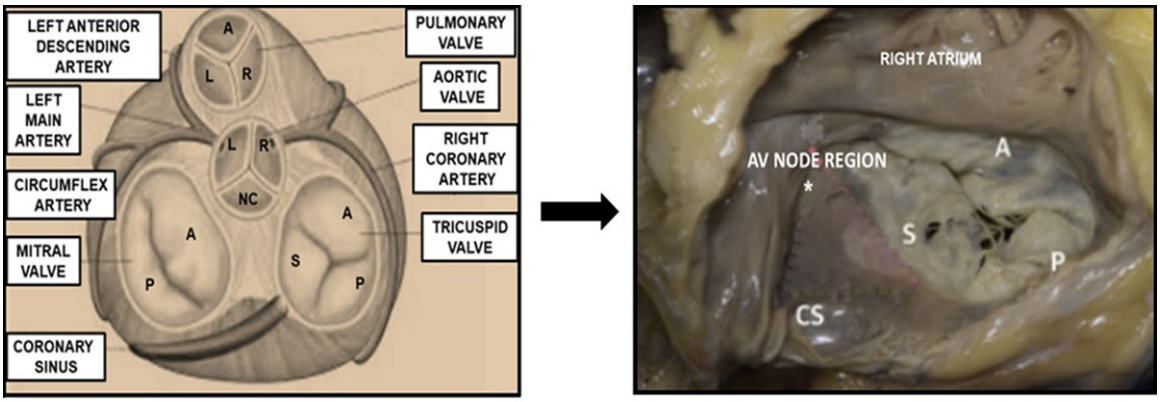

Figure 1. Normal Tricuspid Valve anatomy.

TV annulus is a nonplanar D-shaped structure with an area of 11±2 cm^2, and a diameter of 28±5 mm [7]. The normal decrease in the tricuspid annular area with ventricular systole is 25%. The normal tricuspid annular plane systolic excursion (TAPSE) along the longitudinal axis of the RV is 16 mm [8, 9]. Tricuspid regurgitation is highly dependent on annular dilation and significant TR can occur with only 40% annular dilatation compared with 75% annular dilatation required for mitral regurgitation [10]. A tricuspid annulus diameter during diastole greater than 34 mm or a tricuspid annulus diameter during systole greater than 32 mm are markers of significant TR [7, 9].

The anterior leaflet, which has a quadrangular shape, is the largest leaflet of the TV and has the greatest motion. The posterior TV leaflet, which has a triangular shape, is the shortest leaflet circumferentially and in approximately 10% of patients is not separated from the anterior leaflet. The septal leaflet, which is semi-circular with scallop indentations, is the least mobile of the TV leaflets and is attached to the tricuspid annulus directly above the interventricular septum [7, 9]. The number of leaflets in the TV can vary from three to seven [11, 12]. **Figure 1** illustrates the normal anatomy of the TV and surrounding structures and is adapted from [7, 11, 12].

Under pathological conditions, the TV leaflets have reduced leaflet coaptation that can be either symmetrical, resulting in central TR, or asymmetrical, resulting in eccentric TR [13]. Three important structures lie close to the tricuspid valve. The noncoronary sinus of Valsalva is adjacent to the commissure between the anterior and septal leaflets. The atrioventricular (AV) node is 3 to 5 mm posterior to the anteroseptal commissure [9]. The right coronary artery is only 8.8 mm±4.5 mm from the anterior TV leaflet and 3.6 mm±3.4 mm from the posterior leaflet [7, 14]. See **Figure 1**.

The anterior papillary muscle is the largest papillary muscle in the RV with attachments to the moderator band and with chordae supporting the anterior and posterior leaflets [11]. The posterior papillary muscle gives chordal support to the posterior and septal leaflets. A septal papillary muscle may be small, multiple or absent in up to 20% of normal patients. In this instance, chordae may arise directly from the interventricular septum to the anterior and septal TV leaflets. On average, there are 25 chordal insertions into the TV with approximately seven passing to the anterior leaflet, six to the posterior leaflet, nine to the septal leaflet, and three inserting into the commissural areas [11].

The chordae are divided into primary chordae, which attach to the free edges of the TV, intermediary or secondary chordae, which attach to the basal portion of the ventricular surface of the TV leaflets, and marginal, third-order, or basal chordae, which join the body of the cusp directly to the septum.

Table 1. Tricuspid regurgitation etiologies

Congenital Abnormality	Primary Leaflet Abnormality	Ebstein's Anomaly, Giant right atrium, Marfan's Syndrome
Congenital Abnormality	Acquired Leaflet Abnormality	VSD, Septal Aneurysm, Levotransposition Great Arteries
Acquired Abnormality	Primary Leaflet Abnormality	Myxomatous Degeneration, Rheumatic Heart Disease, Endocarditis, Carcinoid, Endomyocardial Fibrosis, Trauma, Drugs/Toxins, (Fenfluramine and Phentermine)
Acquired Abnormality	Functional (Secondary) Leaflet Abnormality	LV Ischemia/Dysfunction, LV Cardiomyopathy
Acquired Abnormality	Functional (Secondary) Leaflet Abnormality	Ischemic right heart disease, pacemaker lead-induced or cardiac defibrilator lead-induced TR, RV volume overload, RV cardiomyopathy, chest irradiation
Acquired Abnormality	Functional (Secondary) Leaflet Abnormality	COPD, pulmonary emboli, Left to Right shunt, volume overload
Acquired Abnormality	Functional (Secondary) Leaflet Abnormality	Atrial fibrillation

COPD, Chronic Obstructive Pulmonary Disease; LV, Left Ventricle; RV, Right Ventricle; VSD, Ventricular Septal Defect.

Blood flow from the right ventricle into the pulmonary circulation is dependent on a low-impedance, highly distensible pulmonary vasculature and requires in the resting condition only approximately 20% of the LV stroke work. Mild increases in pulmonary artery pressure produce tricuspid annular-right atrial dilation whereas moderate to severe increases in pulmonary artery pressure cause RV dilation [7, 14].

Etiologies

Primary tricuspid regurgitation occurs in 15 to 30% of patients due to the direct involvement of the tricuspid valve and is the result of congenital heart disorders such as Ebstein's anomaly, or acquired disorders or diseases of the TV, such as myxomatous degeneration of the tricuspid valve, endocarditis, carcinoid syndrome, rheumatic heart disease, or chest irradiation [7, 9, 15, 16]. Functional TR can result most commonly from ischemic or nonischemic cardiomyopathies, aortic or mitral valvular disease, or pulmonary disease/pulmonary vascular disease. The prevalence of functional TR increases with age. **Table 1** lists the primary and functional causes of TR and is adapted, in part, from [7, 9, 15].

Tricuspid valve annulus dilation and leaflet tethering due to RV remodeling are the major pathophysiologic mechanisms contributing to functional TR [9]. Tricuspid regurgitation leads to further RV dilation and dysfunction, further tricuspid annular dilatation and TV tethering, and worsening TR. With increasing TR, the RV dilates, causing a shift of the interventricular septum toward the LV [8, 9]. Functional TR can also occur in the setting of lone atrial fibrillation due to enlargement of the tricuspid annulus and the RV basal diameter with normal leaflet length and decreased systolic annular coverage in the absence of significant TV tethering [17].

Mortality

The five-year mortality rate in individuals with isolated primary TR can be ≥48% [18, 19]. In patients with functional TR due to heart failure with reduced ejection fraction (HFrEF), mitral valve regurgitation, elevated systolic pulmonary artery pressure, atrial fibrillation, older age or female sex, the five-year survival rate with medical treatment is 68±1% for patients with trivial TR, 58±2% for patients with mild TR, 45±2% for moderate TR, and 34±4% for patients with severe TR [3, 20, 21].

Clinical risk scores are available to predict the morbidity and mortality in patients undergoing TV interventions. The LaPar Risk Score includes patient age, sex, functional class, LV function, the presence of stroke, hemodialysis, chronic lung disease, reoperation, or elective or emergent valve surgery [22]. A score from 0 to 10+ is associated with a predicted major morbidity risk of 13% to 71% and mortality risk of 2% to 34% [22]. In addition, the TRuE Risk Score, which is based on patient comorbidities and measurements of RV function, is a useful prognostic score for stratifying patient morbidity and mortality for TV interventions [23].

Tricuspid regurgitation symptoms and signs

Symptoms associated with advanced TR include: (1) generalized weakness and fatigue due to decreased cardiac output; (2) right upper quadrant discomfort due to hepatic congestion; (3) dyspepsia, and indigestion with gastrointestinal congestion; and leg edema due to fluid retention.

Table 2. Echocardiographic criteria for grading of Tricuspid Valve regurgitation severity

Parameter	Moderate TR	Severe TR	Torrential TR
TV Morphology	Normal or moderately abnormal	Abnormal, flail, large coaptation defect	Abnormal, Severe coaptation defect
TV Inflow into RV	Normal	E wave dominant	E wave dominant
Color Flow	Moderate size jet	Large central jet or jet impinging on right atrial wall	Extremely large dense jet or eccentric jet impinging on right atrial wall
Vena Contracta width, mm	3.0-6.9	7.0-13	≥21
EROA, mm^2	20-39	≥40	≥80
Regurgitant volume, ml	30-44	≥45	≥75
Regurgitant fraction %	30-39	≥50	≥70
Tethering	Abnormal <8 mm	Abnormal >8 mm	Abnormal >10 mm
RV function	Moderate dysfunction and remodeling	Severe dysfunction and remodeling	Severe dysfunction and remodeling
Hepatic blood flow	Blunted systolic flow	Systolic flow reversal	Severe systolic flow reversal

Vena Contracta: Narrowest central flow region of a TR jet that occurs at or just downstream to the orifice of the TV. EROA: Effective regurgitant orifice area obtained by dividing regurgitant flow volume by the velocity of the TR jet.

Tricuspid regurgitation results in a prominent systolic "C-V" wave in the jugular venous pulse due to retrograde systolic blood flow through the incompetent tricuspid valve into the internal jugular veins. There is often a palpable left parasternal lift due to RV enlargement. On cardiac auscultation, a soft, early or holosystolic murmur may be present at the lower left sternal border, which is augmented with deep inspiration. With tricuspid valve prolapse, a systolic "honk" may be present. However, substantial tricuspid regurgitation may exist without these cardiac ausculatory findings being present [9, 15]. The liver is often enlarged, tender to palpation, and has palpable systolic pulsations. In addition, abdominal distension may be present with ascites and edema present in the legs, ankles, and feet.

Diagnostic techniques

On the electrocardiogram (ECG), RV hypertrophy and "strain", right atrial enlargement, and right axis deviation can be clues to TV disease. However, frequently there are no specific markers of tricuspid valve disease on the ECG. In this instance, exercise testing is useful in assessing the exercise capacity in patients with severe TR but with no or minimal symptoms.

Signs of TR on the chest radiograph are often subtle but can include right atrial enlargement, RV enlargement, decreased prominence of the pulmonary vaxculature, enlargement of the superior and inferior vena cava, and distension of the azygos vein.

Two- and three-dimensional transthoracic echocardiography (TTE) are useful in differentiating primary from functional TR. In addition, echocardiography is extremely helpful in the evaluation of TR severity, measurement of the RA, tricuspid annulus, RV and inferior vena cava (IVC) sizes, assessing RV systolic contractility, estimating pulmonary artery systolic pressure, and characterizing LV disease. Tricuspid valve regurgitation is detected using color Doppler imaging and can be semi-quantitated based on the extent of the penetration of the TR jet into the right atrium and inferior vena cava. **Table 2** lists the echocardiographic criteria for grading TR severity, which is adapted in part from [24-27]. Measurements should be determined by a transthoracic echocardiogram before TV intervention because intraoperative transesophageal echocardiography (TEE) evaluation of TR may be affected by the anesthetic vasodiltory effects on pulmonary and systemic vascular resistances.

The vena contracta width measurement is not valid for multiple TR jets into the right atrium. In addition, small errors in the measurement of the vena contracta can result in large errors in the estimation of TR [8].

Leaflet tethering can be quantified in terms of the "tenting distance", or the orthogonal distance between the plane of the TV annulus and the point of leaflet coaptation, and by the tenting area at end-systole by 2D TEE and tenting volume by 3D TTE. Severe, functional TR is accompanied by a tethering distance of

≥10 mm, a tented area >1.6 cm^2, and a tented volume ≥2.3 mL [3, 13]. Currently, echocardiographic quantification of the RV lateral wall strain is under investigation as a gauge of RV function [28].

Established risk factors for progression of TR if left untreated include tricuspid annulus dilation >40 mm in diameter or 21 mm/m^2 on TTE measured at end-diastole; an intercomissural distance >70 mm, RV dysfunction or remodeling, leaflet tethering height ≥5 mm, pulmonary artery hypertension, atrial fibrillation, and an intra-annular RV pacemaker lead or a cardioverter-defibrillator lead [29].

In patients with poor 2D TTE imagines of the TV and when 3D echocardiography is not available for assessing the TV, RV volumes and function, cardiac magnetic resonance (CMR) imaging is useful in the assessment of the TV and RV morphology and function [30-32]. Quantification of TR by CMR is commonly performed by calculating the TR volume as the difference between the planimetered RV stroke volume and forward pulmonic flow volume. More recently, direct measurements of the TR volume have become available with CMR 4D flow techniques [33]. CMR can also reliably measure and track RV remodeling, RV end-systolic volume index, and RV ejection fraction, which is helpful in the determination of the timing of tricuspid valve surgery or predicting cardiac mortality [32].

Right and left heart catheterization should be performed when there is inconsistency between the clinical findings and the results of non-invasive tests to rule out primary pulmonary or LV etiologies as the cause of the patient's symptoms. In addition, coronary angiography, or computed tomographic coronary angiography, should be performed in the evaluation and treatment of patients with TR with coronary risk factors, suspected or known coronary artery disease, and/or cardiomyopathy.

A multidisciplinary heart team that includes a cardiothoracic surgeon, an interventional cardiologist, an echocardiographer, an anesthesiologist, and the patient's primary physician is recommended to property treat high-risk patients with severe TR.

Medical management

Patients with TR and ischemic or non-ischemic cardiomyopathy are managed according to current American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) heart failure guidelines [29, 34, 35]. The management consists of diuretics and angiotensin-converting enzyme (ACE) inhibitors which may ameliorate TR associated with chronic congestive heart failure and fluid overload. If kidney function is preserved in patients with TR, the addition of an aldosterone antagonist, such as spironolactone or eplerenone, is a treatment option, especially for patients with hepatic congestion and secondary hyperaldosteronism.

Patients with primary pulmonary hypertension can benefit from treatment with calcium channel antagonists, endothelin receptor antagonists, phosphodiesterase type five inhibitors and guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin receptor agonists [36]. Anticoagulation with either a direct-acting anticoagulant or with warfarin should be initiated in patients with right heart dilatation due to pulmonary embolism. In patients with atrial fibrillation, anticoagulation and other pharmacologic therapy or electrical cardioversion for rhythm control can be useful because restoration of normal sinus rhythm and reduction in right atrium (RA) size can be effective in reducing TR.

Surgical tricuspid valve intervention

Mild or moderate degrees of functional TR, if left uncorrected at the time of left-sided valve surgery, can progress in ≥25% of patients and result in increased heart failure hospitalizations, decreased long-term functional outcome, and decreased survival [4-6]. Conversely, tricuspid valve repair during mitral or aortic valve surgery is associated with improved functional outcomes and a decrease in cardiac-related mortality [37, 38]. Tricuspid valve repair during left-sided heart surgery does not significantly increase the risk of postoperative morbidity or mortality in patients with preserved RV dimensions and function [35, 35A]. Tricuspid valve surgery should also be considered in patients with severe TR after prior left-sided surgery if the patients are symptomatic and progressive RV dilatation or dysfunction is evident and

recurrent left-sided valve or LV dysfunction and severe pulmonary vascular disease or pulmonary hypertension have been excluded [39]. Isolated TV surgery for severe TR is best performed when patient symptoms are not responsive to medical therapy and before the onset of RV dysfunction. Surgery for patients with symptomatic TR late after left-sided valve surgery can be associated with mortality rates ≥20-30% primarily due to RV dysfunction and patient comorbidities [36, 40]. However, in high-risk patients with EuroSCOREs of 7.8±1.4, minimally invasive tricuspid valve surgery through a right thoracotomy is a treatment option that can be associated with in-hospital and 30-day mortalities of ≥3% [41]. Nonetheless, the advantages and disadvantages of tricuspid valve surgery should be carefully discussed with patients with TR with significant RV systolic dysfunction and/or pulmonary hypertension because of the possibility of RV failure after TV surgery.

The principles of TV surgical reconstruction are to: (1) restore full leaflet mobility; (2) correct leaflet prolapse; (3) establish large leaflet coaptation; and (4) reduce and stabilize the TV annulus. Surgical TV repair with annuloplasty of an annulus that is ≥40 mm in diameter or >21 mm/m^2 is the preferred treatment for functional TR [36, 42]. Annuloplasty is usually performed by implantation of a rigid, semi-rigid, or flexible ring in the TV annulus. With rigid TV rings the dimension of the septal annulus is better stabilized, thereby reducing the possible recurrence of TR. The angioplasty rings or bands are open at the septal annulus area to avoid injury to the atrioventricular node (AV) node and the His conduction system. Recently, tricuspid rings that resemble the complex three-dimensional configuration of the native tricuspid annulus have been developed and are used for tricuspid annuloplasty [43]. In general, ring annuloplasty of the TV is preferred over direct suture annuloplasty because of the decreased incidence of residual or recurrent TR and the need for reoperation and increased patient survival [44].

Patients with leaflet tethering should also undergo a leaflet procedure such as edge-to-edge repair or alternatively TV replacement [45, 46]. If feasible, TV repair rather than replacement should be employed, including resection of diseased leaflet tissue, Gore-Tex® chord replacement, and pericardial leaflet reconstruction [39, 44]. For pacemaker lead-induced severe TR, surgical repair of the TV should be considered with concomitant removal of the RV pacemaker lead and implantation of an epicardial lead in order to reduce the risk of late recurrence of the TR. Five and ten-year survival rates after tricuspid repair range from 64 to 72% and 44 to 47%, respectively, and are dependent on the patient's preoperative LV and RV function and New York Heart Association (NYHA) functional class [45, 46].

TV replacement should be considered when TV repair is technically not feasible or in patients with significant degeneration of the tricuspid valve leaflets, substantial RV remodeling and RV dysfunction in which TV coaptation is absent, or in patients with pulmonary hypertension [37].

Studies comparing bioprosthetic and mechanical valves for tricuspid valve replacement indicate similar long-term outcomes. Many surgeons favor bioprosthetic valves over mechanical prosthetic valves because of the lower risk of thrombosis and embolism and the lack of requirement for chronic anticoagulation with bioprosthetic valves. However, the choice of a prosthetic valve should be individualized and is dependent on the patient's age, physical condition, and concomitant cardiac and non-cardiac diseases [36]. In patients who are less than 60 years of age and who do not have a contraindication to anticoagulation, a mechanical tricuspid prosthesis is recommended because of the increased longevity of mechanical prosthetic valves over bioprosthetic heart valves [21]. The incidence of permanent pacemaker implantation in patients after TV replacement can be as high as 34% in comparison with an incidence of 10.9% after isolated TV repair [47]. The ten-year survival rates after TV replacement range from 30% to 50%, and the late mortality is predicted by the patient's preoperative functional class, the LV and RV function, and prosthesis-related complications [37, 48, 49]. Echocardiographic evaluation of the TV hemodynamics is recommended six weeks to three months after TV implantation or TV repair and every 12 months thereafter. In addition, echocardiography is recommended whenever

patient symptoms or signs significantly change and are persistent.

Box 1. Summarizes the American Heart Association/American College of Cardiology (AHA/ACC) and the ESC Guidelines for surgical interventions in patients with functional TR. Adapted from [29, 34, 35, 42].

Box 1.

1. Tricuspid valve surgical repair or replacement is recommended for patients with severe TR who are undergoing left-sided valve surgery.

2. Tricuspid valve surgical repair or replacement can be beneficial for patients with symptoms and signs due to severe TR that are unresponsive to medical therapy.

3. Tricuspid valve surgery at the time of left-sided valve surgery can be beneficial for patients with mild, moderate, or severe functional TR with either 1) tricuspid annular dilation or 2) prior evidence of right heart failure.

4. Tricuspid valve surgery should be considered for patients with moderate functional TR and pulmonary artery hypertension at the time of left-sided valve surgery.

5. Surgery should be considered in patients with mild or moderate TR, even in the absence of TV annular dilation, but who have had recent right heart failure and are undergoing left heart surgery.

6. In patients who have undergone previous left-sided valve surgery and who do not have severe pulmonary hypertension or significant RV systolic dysfunction, reoperation is a therapeutic option for isolated tricuspid valve repair or replacement because of persistent symptoms and signs due to severe TR despite medical therapy.

Transcatheter tricuspid regurgitation treatment

Patients with functional TR with a LV ejection fraction <40%, severely impaired RV function, and pulmonary hypertension are at high risk for surgical TV repair or replacement because of increased patient morbidity or mortality. In these patients, transcatheter TV repair or replacement is a therapeutic option. Patient selection is exremely important. In addition, comprehensive computed tomography and/or echocardiography is crucial for deciding which procedure and which device is most appropriate for the individual patient with TR. Five types of transcatheter devices are currently being evaluated for the treatment of severe TR in these patients: 1) TV edge-to-edge repair using the MitraClip or TriClip (Abbott Vascular) or the Pascal clip (Edwards Lifesciences); 2) The FORMA spacer device (Edwards Laboratories) that occupies the TV EROA and provides a surface for native TV leaflet coaptation; 3) The TriAlign and Cardioband devices designed to decrease the TV annulus dimensions in order to reduce TR severity; 4) Tric Valve implants at the entrances of the superior vena cava (SVC) and IVC into the right atrium or the Sapien valve in the IVC to prevent blood regurgitation into the vena cava, hepatic veins and hepatic congestion due to severe TR; 5) Implantation of a prosthetic Gate valve, Cardiovalve, EVOQUE, or Intrepid valve into the native TV. **Figure 2** illustrates the transcatheter devices currently available for TV coaptation, annuloplasty, or vena cava valve insertion. The primary challenge in the development and utilization of these devices is the complexity of the TV anatomy and the closeness of the atrioventricular node, the coronary sinus, the right coronary artery, and the aortic valve to the TV. Transesophageal echocardiography and/or intracardiac ultrasound and fluoroscopy are used to achieve the most optimal visualization of the TV during transcatheter repair or replacement. In patients with severe TR who are at significant risk for postoperative bleeding, TV repair is preferable over TV replacement because lifelong anticoagulation is not necessary after TV repair but is necessary after TV replacement. See **Figure 2**.

The transcatheter TV repair with the MitraClip system is the most common device used to date, primarily because of the extensive experience acquired with the use of this clip in the treatment of patients with mitral regurgitation. The Mitraclip can be repositioned or removed, and additional clips can be implanted to achieve adequate TR reduction. In the Tricuspid Valve (TriValve) registry and other investigations, the MitraClip device has been used in 80% of patients for the treatment of TR [50-53]. Recently, the clip has been modified to produce the TriClip in order to facilitate the bending and maneuverability of the device in the RA

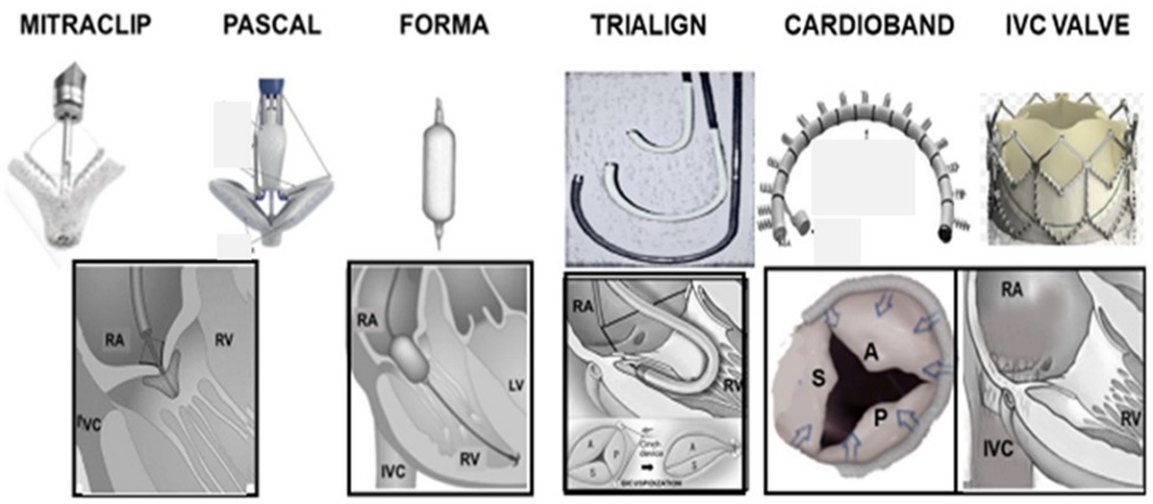

Figure 2. Transcatheter devices for TV coaptation, annuloplasty, or vena cava valve insertion. Device figures reproduced with permission from the manufacturers.

Table 3. Transcatheter devices for Tricuspid Valve regurgitation

Transcatheter Device	Investigation	Device Success Rate	Complications	Mortality	Clinical Trial Investigations
Mitraclip/Triclip (Abbott Vascular)	Trivalve Registry [51-53]; Clinical Reports [56, 57]	≥90%	Clip entrapment in chordae; Clip detachment	30-day: 2.8%; 6-months: 16.0%; 1-year: 37.5%	Triluminate [58]
Pascal (Edwards Lifesciences)	Clinical Reports [59, 60]	82-90%	Clip entrapment in chordae; Clip detachment	1 year: 7%	Clasp Trial [61]
Forma (Edwards Lifesciences)	Clinical Reports [62, 63]	89%	RV perforation with NitinoL anchor	1-year: 0%; 2-2.5 year: 24%	Spacer Trial [64, 65]
Trialign (Mitralign INC.)	Scout Trial [66] TriValve Registry [51]	80%	Right coronary artery injury; Pleget detachment from annulus	30-day: 0%	Scout-II Trial [67]
Cardioband (Edwards Lifesciences)	Tri-Repair [68, 69] Trivalve Registry [51]	≥93%	Bleeding complications due to multiple anchors; Right coronary artery injury	6-months: 10%; 1-year: 17%	TriBand [69, 70]

and TV coaptation. The majority of the clip procedures are performed through the right femoral vein in order to access the RA with the patient under general anesthesia. See **Figure 2**.

In the transcatheter TV clip repair, the first therapeutic target is the implantation of a clip close to the anteroseptal commissure, where the coaptation deficit is minimal, in order to approximate the leaflets and facilitate the implantation of additional clips along the coaptation line. However, there is a risk in this area of clip entrapment in the chordae or chordal injury because chordae density is greatest at the commissural region. Tricuspid valve conditions that make leaflet clipping unsuccessful include an effective regurgitant orifice area (EROA) >1.5 cm^2, a TV coaptation defect >15 mm, and TR caused by markedly restricted leaflet mobility due to pacemaker or implantable cardioverter-defibrillator wires embedded across the TV [53].

High-risk patients with very large TV coaptation defects may not be treatable solely with a leaflet clip device. For such patients, an alternative device is the transcatheter FORMA device, which is a spacer device that occludes the large central TV coaptation defect. See **Figure 2**.

An alternative treatment is a catheter-based TV annular reduction with the TriAlign or the Cardioband devices, followed by transcatheter leaflet coaptation with clip(s) treatment if necessary. For patients with significant lead-induced TR, without significant TV or pacemaker wire immobility, TV repair can be considered with concomitant wire removal and epicardial implantation of the pacemaker wire in order to

reduce the late recurrence of TR. **Table 3** lists the currently available transcatheter coaptation and annuloplasty devices, the reported success rates with implantation of the devices, the morbidity and mortality associate with the procedures, and the clinical trials with the devices. Many of the clinical trials that are listed in **Table 3** represent transcatheter device feasibility and safety trials. **Table 3** is adapted in part from [54, 55].

MitraClip

The results of 249 patients with TR that have undergone the edge-to-edge TV repair with the MitraClip device in the Tricuspid Valve (TriValve) registry have been reported [71]. The mean patient age was 77±9 years and the median EuroSCORE of these patients was 6.4%. Procedural success with a reduction of TR to ≤ grade 2/4 was achieved in 77% of patients. On average, 2±1 clips were placed, primarily in the TV anteroseptal commissure. Predictors of procedural failure included the absence of a central and/or anteroseptal location of the TR, a coaptation gap size ≥6.4 mm, an EROA ≥0.70 cm^2, and a tricuspid tenting area ≥3.2 cm^2 [71]. No procedural deaths occurred but seven patients died in the hospital. After a median follow-up of 290 days, an improvement of at least 1 NYHA class grade occurred in 72% of the patients. At one year followup, TR reduction, evaluated by echocardiography, was sustained in 84% of patients, all-cause mortality was 20%, and the combined rate of mortality and unplanned hospitalization for heart failure was 35% [71]. Predictors of one-year mortality after transcatheter edge-toedge valve repair included procedural failure, absence of sinus rhythm, and decreased renal function.

The Trial to Evaluate Treatment With Abbott Transcatheter Clip Repair System in Patients With Moderate or Greater Tricuspid Regurgitation (TRILUMINATE) trial, a prospective, international study investigated the safety and efficacy of the TriClip Tricuspid Valve Repair System (Abbott Vascular) in patients with moderate or severe TR with primary (10 patients), functional TR (71 patients), or mixed disease (3 patients) [58, 72]. The mean EuroSCORE II score in these patients was 8.6%. The clip implant success rate was 100%. Implantation of one clip occurred in 17 patients, two clips in 40 patients, 24 patients received three clips, and four patients received four clips [58, 72].

At one year after the clip procedure, TR was reduced to moderate or less in 71% of the patients [72]. The TV EROA was reduced from 0.65±0.29 cm^2 to 0.35±0.23 cm^2 at 6 months. Eighty-three percent of the patients increased their 6-minute walk test from 272.3±15.6 to 303.2±15.6 meters and improved their Kansas City Cardiomyopathy Questionnaire score by 20±2.6 points. A single leaflet device detachment occurred in one patient without worsening of TR. One-year all-cause mortality was 7.1% with cardiovascular mortality in 4 patients, myocardial infarction in 1 patient, stroke in 1 patient, and new-onset renal failure in 1 patient [72]. The TriClip G4 device is currently being evaluated in the bRIGHT registry.

PASCAL device

The PASCAL clip device (Edwards Lifesciences) has two clasp arms that can be opened or closed independently and a central 10 mm spacer to reduce the TV EROA, which makes this device more suitable for patients with complex TV anatomy. The results from the clinical trial of the transcatheter valve repair system in tricuspid regurgitation (CLASPII) have been presented at the EuroPCR 2021 [73]. In 63 patients with severe TR who underwent insertion of the Pascal device, 89% improved by at least one TR grade and 70% saw at least a two-grade reduction in TR with significant gains in quality life on the Kansas City Cardiomyopathy Questionnaire. Two patients died of cardiovascular causes. Severe bleeding occurred in five patients, while re-intervention related to the device and major access-site vascular complications requiring intervention occurred in one patient.

A comparison has been reported between 32 patients with TR treated with the PASCAL device and 88 patients with TR treated with the Mitraclip XTR device [60]. Although the patients in the PASCAL group exhibited greater baseline TR severity, the procedural success rate in these patients was 90.6% in comparison with a procedural success in 86.4% in the MitraClip XTR treated patients. The differences in procedural success with the Pascal and MitraClip

device were not statistically significantly different.

These investigations indicate that transcatheter TV edge-to-edge repair is feasible and is associated with patient functional improvement. Additional prospective randomized studies that compare the TriClip or the Pascal device with optical medical therapy and alternative repairs are indicated to fully assess the safety, durability, and chronic efficacy of the clip devices.

Forma device

The FORMA system (Edwards Lifesciences) consists of a foam-filled balloon 42 mm in length which is placed in the TV EROA, thereby reducing the gap in leaflet coaptation. The device which is inserted via the subclavian or axillary vein is secured to the RV apex by a nitinol anchor. Although severe TR is reduced with this device from 95% at baseline to 33% at 2-3 years, as many as two-thirds of the patients can have persistent significant TR [74]. Two procedural deaths have occurred with this device due to RV perforation by the nitinol anchor. The steerable guide sheath has been revised to facilitate coaxial alignment with the tricuspid annulus and an apposition indicator has been added to ensure a more predictable and safe anchoring of the device in the RV apex [74]. Although the results of the SPACER trial will further address the safety, efficacy, and durability of the FORMA device [74, 75], this device is no longer available for implantation by physicians in patients with TR.

Cardioband device

The Cardioband System (Edwards Lifesciences) is an adjustable C-shaped ring that is implanted in the tricuspid annulus by positioning the 12-18 anchors of the ring in the anterior and posterior portion of the TV annulus. After the positioning of the anchors in the TV annulus, traction on the device decreases the diameter of the annulus by approximately 9-16% and thereby decreases the grade of TR. The initial results of the Triband Study in 61 patients with severe and symptomatic functional TR who had not responded to diuretic therapy have been reported [76]. Following the insertion of the Cardioband device, 78% showed a reduction of at least one grade in TR. However, 59% of the patients had moderate-or-low-grade TR. TV septal-lateral annular diameter decreased by 20%. At 30-day follow-up, there was one MI but no CV mortality or stroke [76]. The most common complications of the procedure were severe bleeding in seven patients, major access-site/vascular complications in four patients, coronary artery injury requiring intervention in four patients; and requirement for renal replacement therapy in two patients. Seventy-four percent of the patients improved to NYHA class I-II and the overall Kansas City Cardiomyopathy Questionnaire score improved by 17 points [77]. A European, prospective, single-arm, multicenter follow-up Tricuspid Cardioband Reconstruction System (TriBAND) study is in progress that involves patients who will be followed up for 5 years to evaluate the safety and efficacy of the Cardioband TR system in symptomatic patients with chronic, moderate-to-severe functional TR [78].

Although implantation of Cardioband is feasible, there is only a moderate decrease in the TR with this device. The current requirement for multiple anchors to secure this device to the TV annulus, which increases the risk of bleeding and tissue damage, is an important challenge for the designers of this device to overcome in order for the device to become routinely utilized in high-risk patients with severe TR.

Trialign

The transcatheter TriAlign plication system attempts to replicate the results of the surgical Kay TV bicuspidization TV procedure [66, 67, 79]. This technique is performed by placing a double pledget-supported mattress suture from the anteroposterior commissure to the posteroseptal commissure along the posterior annulus. A dedicated plication device is used to draw the anteroposterior pledget toward the posteroseptal pledget and lock the suture. The Symptomatic Chronic Functional Tricuspid Regurgitation 1 Trial (NCT02574650) in 15 patients with TR, demonstrated an acute implant success in all patients [66, 67]. One patient required right coronary artery stenting due to coronary artery damage. The technical success rate at 30 days was 80%, with 3 single-pledget detachments without necessitating patient re-intervention [66]. In the remaining 12 patients, the TV annulus was reduced from 12.3±3.1

cm^2 to 11.3±2.7 cm^2 and the EROA was decreased from 0.51±0.18 cm^2 to 0.32±0.18 cm^2, while the LV stroke volume increased from 63.6±17.9 ml to 71.5±25.7 m [66].

At present, additional trials of transcatheter TV repair devices are required to demonstrate the safety of this technology, quantify the decrease in TR severity, and assess the long-term durability, efficacy and outcome of the interventions on patient symptoms and quality of life. The TriClip and Pascal clip devices appear to be most likely to achieve the greatest clinical utility.

Transcatheter tricuspid valve replacement

In high surgical risk patients in whom transcatheter TV repair is not possible due to a TV coaptation gap >8 mm, large TV annular size, noncircular annuli, or torrential TR where the severity of the TR cannot be optimally reduced with clip devices, transcatheter TV replacement (TTVR) is emerging as a treatment option. There are two broad categories of TTVR: heterotopic replacement, where a valve is deployed in one or both vena cavae, or orthotopic TV replacement, where a new valve is deployed at the site of the native TV.

Heterotopic TTVR

Caval valve implantation of a prosthetic valve, such as the Sapien Valve or the TricValve, can reduce TR into the vena cava and hepatic congestion [80]. In the TRIcuspid Regurgitation in Patients With Advance Heart Failure With Caval Vein Implantation of the Edwards Sapien XT Valve (TRICAVAL) trial, the Sapien XT valve has been implanted in the IVC in patients with severe TR who are at high risk for surgical procedures [81]. Insertion of the Sapien XT valve improved patient NYHA class, dyspnea, and quality of life at three months after the valve intervention. However, there were no statistically significant differences in comparison with patients treated with optimal medical therapy in the six-minute walk test, NYHA class, NT-proBNP concentrations, right heart function, or heart failure hospitalizations [81]. Moreover, the trial has been terminated for safety reasons due to valve dislodgement in four out of 14 patients. Currently, the Heterotopic Implantation of the Edwards-Sapien Transcatheter Aortic Valve in the Inferior Vena Cava for the Treatment of Severe Tricuspid Regurgitation (HOVER) trial is evaluating the safety, efficacy, and quality of life in six patients who have undergone the Sapien XT valve implantation in the IVC for treatment of severe TR [82].

The Transcatheter Bicaval Valves System in the Superior and Inferior Vena Cava in Patients With Severe Tricuspid Regurgitation (TRICUS) trials in the United States and Europe are evaluating in patients with severe TR at high risk for surgical procedures the feasibility, safety, and efficacy of TricValves (P+F Products + Features GmbH), which are self-expanding bovine pericardial tissue valves mounted on nitinol stents, that are placed in the SVC and IVC [83]. The results of the TRICUS studies, which are currently being evaluated, will determine whether the benefits of heterotopic valve insertion significantly outweigh the clinical risks. Heterotropic valve insertion in the vena cavae is more challenging than orthotopic TTVR because of the variation in size of the IVC and SVC, the risk of valve thrombosis and embolization, the dislodgement of the valve(s), and the risk of hepatic vein occlusion.

Orthotopic TV replacement: Gate valve, Cardiovalve, Evoque, and Intrepid valves

High surgical risk patients with severe TR due to cardiomyopathies, rheumatic heart disease, infective endocarditis, or RV pacemaker or defibrillator wires are potential candidates for TTVR. In addition, patients with a coaptation gap >8 mm between TV leaflets, calcification in the TV leaflets, immobile or severely retracted septal or other TV leaflets or non-central TV regurgitant jet(s) are unlikely to have good outcomes with TV repair and are candidates for TTVR [29].

In order to determine which valve is the most appropriate device for a high-risk patient with TR, the TV leaflet anatomy, the TV annular size, the angle of the inferior vena cava entering the RA and the femoral access must be carefully evaluated by TEE, gated CT scan, and color Doppler examination. Improper valve anchoring in the tricuspid annulus can lead to device malfunction, paravalvular leak, valve embolism, or valve thrombosis. The GATE TTVR system (NaviGate Cardiac Structures), the Cardiovalve (Boston Medical), the EVOQUE valve (Edwards Lifesciences), or the Intrepid valve (Medtronic)

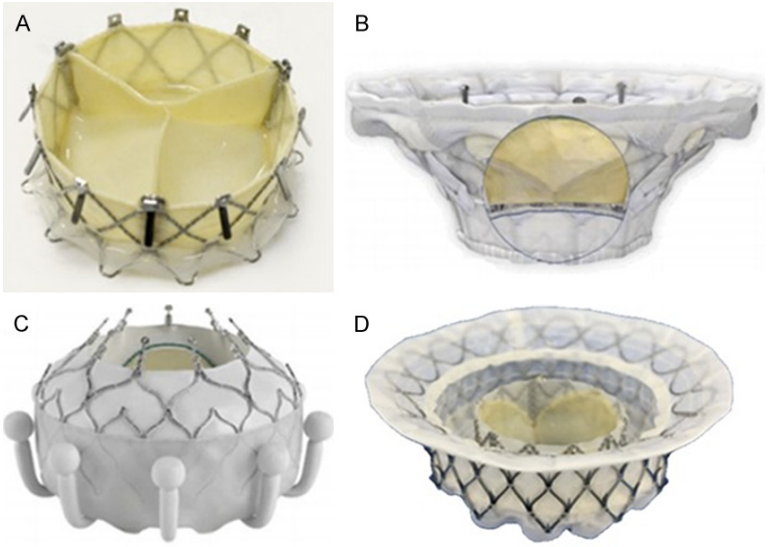

Figure 3. Transcatheter TV replacement valves: Gate (A), Cardiovalve (B), Evoque (C), Intrepid (D) Valves. Valve figures reproduced with permission of the manufacturers.

have delivery systems with intricate steering devices to facilitate transcatheter TV insertion. The Intrepid valve does not require leaflet capture to be deployed. **Figure 3** shows each of these TTVR valves.

Gate valve

The GATE valve (NaviGate Cardiac Structures) is a self-expanding sutureless valve-in-stent designed for TTVR. The valve consists of three pericardial leaflets in a self-expanding nitinol stent with 12 atrial winglets and ventricular anchors to ensure fixation. The early compassionate-use experience has been associated with a procedural success in 77% of 34 patients, with residual ≤2+ TR in all patients [84]. Surgical conversion was required in 14% of the patients, and 30-day mortality was ~13% due to advanced RV dysfunction and patient comorbidities [84]. Larger studies of patients with longer follow-up are needed to further evaluate the outcomes of the GATE device in TTVR.

Cardiovalve

Cardiovalve (Boston Medical) is composed of bovine pericardial leaflets mounted on a nitinol frame. Valve anchoring is achieved via grasping of the TV leaflets and is assisted by an anchoring and sealing element [85, 86]. A feasibility trial (NCT04100720) with the Cardiovalve in 15 NYHA Class II-IVa patients with a LV ejection fraction of ≥35% is planned in the U.S. [86].

Evoque valve

The Evoque tricuspid valve (Edwards Lifesciences) is composed of bovine pericardial leaflets with an intra-annular sealing skirt and TV anchors. See **Figure 3**. The safety and effectiveness of the Evoque valve are being evaluated in the TRISCEND trial in patients with severe TR treated with optimal medical therapy (OMT) compared with patients treated with OMT alone [87]. Initial results have been presented at the EuroPCR 2021 [87]. TRISCEND enrolled 56 patients in whom 92% had at least severe TR and 84% were NYHA functional class III-IV. For 68%, the etiology of TR was functional, whereas 11% had degenerative TR and the rest had mixed origins. At the 30-day follow-up after implantation of the Evoque valve, 98% had mild or none/trace TR. Seventy-five percent were NYHA class I-II with significant improvements in 6-minute walk distance and Kansas City Cardiomyopathy Questionnaire score. At the 30 day follow-up, one patient had died of a cardiovascular cause. Severe bleeding due to anticoagulation occurred in 12 patients, while two patients required urgent tricuspid valve re-intervention and one patient had major access-site/vascular complications. Two patients died for an all-cause mortality rate of 3.8%. Based on the results of this study, TRISCEND II has been initiated [88].

Intrepid valve

The Intrepid Valve (Medtronic) is a dual-stent system with a 29 mm bovine pericardial valve. Transfemoral insertion is through a 35Fr delivery system. An early feasibility trial with the Intrepid valve for TTVR is scheduled to start in the United States through the FDA breakthrough Device Program and is based on the

successful insertion of the valve in three high-risk patients with severe TR [89].

TTVR is an emerging investigational therapy for patients with severe functional TR who are not candidates for transcatheter TV repair or surgical valve repair or replacement and would otherwise have a dismal prognosis. Transcatheter TV replacement is less dependent on the TR etiology or the leaflet morphology than the transcatheter repair devices and the procedure is not associated with the morbidity and mortality associated with open-heart surgery. The primary challenges for TTVR for high-risk patients with severe TR are the large device size required for insertion into dilated TV annuli and the requirement for chronic anticoagulation therapy. In patients with TR at significant risk for bleeding, a TV repair strategy is preferable to TTVR. Severe RV dysfunction and severely increased pulmonary vascular resistance are absolute contraindications to TV repair or replacement because of concerns regarding post-procedure right heart failure. TTVR design improvements are currently needed to reduce the vascular sheath size and the deliverability of the prosthetic TVs.

Summary and future perspectives

Functional TR is the most common form of TR and is caused by dilation of the TV annulus and RV leaflet tethering due to ischemic and non-ischemic cardiomyopathies, left-sided valve disease, or RV dilation from severe pulmonary disease with pulmonary hypertension. The five-year survival of patients with severe TR and HFrEF with medical treatment is 34%. A multidisciplinary heart team approach is recommended to properly treat patients with severe TR. Medical management consists of the administration of diuretics, angiotensin-converting enzyme (ACE) inhibitors, and aldosterone antagonists. In patients with TR and atrial fibrillation, rhythm control with pharmacologic therapy or electrical cardioversion to sinus rhythm can be useful.

Tricuspid valve surgery is a therapeutic option for symptomatic patients with progressive RV dilatation or dysfunction without severe LV dysfunction and/or severe pulmonary vascular disease/hypertension. Surgical repair with ring annuloplasty is the preferred treatment. Patients with leaflet tethering should also undergo an edge-to-edge repair or alternatively valve replacement. TV replacement should be considered when TV repair is not feasible or in patients with significant intrinsic disease of the TV leaflets, substantial RV remodeling, or in patients with moderate pulmonary hypertension.

Transcatheter TV repair or replacement is possible in high-risk patients with an LV ejection fraction <40%, dilated tricuspid annulus and right heart chambers, and impaired RV function. In high-risk patients in whom TV repair is not possible, transcatheter valve insertion is emerging as a treatment option. Whether transcatheter devices will significantly decrease patient mortality and improve patient quality of life will be determined by the current and future pivotal clinical trials.

Devices for transcatheter tricuspid valve repair, annuloplasty, and transcatheter tricuspid valve replacement for high-risk patients with functional TR will continue to be developed and be perfected and the clinical indications for these devices will be expanded. Ultimately transcatheter tricuspid valve repair or replacement will become an important part of guideline-directed therapy for high-risk patients with chronic functional TR.

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Disclosure of conflict of interest

None.

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