Diagnosis and treatment of tricuspid valve disease: current and future perspectives

Josep Rodés-Cabau, Maurizio Taramasso, Patrick T O'Gara

The assessment and management of tricuspid valve disease have evolved substantially during the past several years. Whereas tricuspid stenosis is uncommon, tricuspid regurgitation is frequently encountered and is most often secondary in nature and caused by annular dilatation and leaflet tethering from adverse right ventricular remodelling in response to any of several disease processes. Non-invasive assessment of tricuspid regurgitation must define its cause and severity; advanced three-dimensional echocardiography, MRI, and CT are gaining in clinical application. The indications for tricuspid valve surgery to treat tricuspid regurgitation are related to the cause of the disorder, the context in which it is encountered, its severity, and its effects on right ventricular function. Most operations for tricuspid regurgitation are done at the time of left-sided heart valve surgery. The threshold for restrictive ring annuloplasty repair of secondary tricuspid regurgitation at the time of left-sided valve surgery has decreased over time with recognition of the risk of progressive tricuspid regurgitation and right heart failure in patients with moderate or lesser degrees of tricuspid regurgitation and tricuspid annular dilatation, as well as with appreciation of the high risks of reoperative surgery for severe tricuspid regurgitation late after left-sided valve surgery. However, many patients with unoperated severe tricuspid regurgitation are also deemed at very high or prohibitive surgical risk. Novel transcatheter therapies have begun to emerge for the treatment of tricuspid regurgitation in such patients. Experience with such therapies is preliminary and further studies are needed to determine their role in the management of this disorder.

Published **Online**
April 2, 2016
http://dx.doi.org/10.1016/S0140-6736(16)00740-6

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Introduction

Management of tricuspid valve disorders has traditionally been accorded lesser importance than that of left-sided valvular heart disease. The tricuspid valve has been referred to as the "forgotten valve". Recently, increased understanding of the long-term adverse consequences of tricuspid valve disease, and in particular of severe tricuspid regurgitation,[1] coupled with continued advances in surgical and percutaneous transcatheter techniques, has led to more aggressive treatment recommendations. There is widespread recognition, however, that the evidence base underlying current guideline recommendations for management of patients with tricuspid valve disease does not include any sufficiently rigorous randomised controlled trials (RCTs) to inform clinical practice.[2,3] As is true for most areas of valvular heart disease, there is an urgent need for additional, prospective research on the diagnosis and treatment of tricuspid valve disease.

Functional anatomy and pathophysiology

The three sail-like leaflets of the tricuspid valve are designated as anterior, posterior, and septal (figure 1). Individual sizes vary, but the anterior leaflet predominates. The leaflets are attached by chordae to their respective right ventricular papillary muscles. A distinct septal papillary muscle is absent in about 20% of people.[5] In many instances, it is represented by a group of small muscles of variable size and shape. By contrast with their mitral valve counterparts, tricuspid valve chordae also attach directly to the right ventricular endocardium. The tricuspid annulus is an ellipsoid, saddle-shaped structure that becomes more circular as it dilates in an anterior-posterior direction in response to right ventricular enlargement. The integrity of the tricuspid valve apparatus is closely related to right ventricular size and function. Volume overload of the right ventricle (such as with tricuspid regurgitation or a large atrial septal defect) or pressure overload of the right ventricle (such as with pulmonic valve stenosis or pulmonary artery hypertension), or both, can impair tricuspid valve function. With chronic volume overload, the right ventricle dilates and can become hyperdynamic. Right ventricular hypertrophy in response to chronic pressure overload can help to maintain ejection performance. However, the right ventricle is exquisitely sensitive to acute pressure overload, as for example with massive pulmonary embolism, in which acute right ventricular failure can be seen with mean pulmonary artery pressures of 30–35 mm Hg. With tricuspid stenosis, a pressure gradient exists between the right atrium and ventricle, resulting in progressive degrees of right atrial hypertension. Advanced tricuspid valve dysfunction can lead to right heart failure as manifested by hepatic enlargement, ascites, oedema, and low output syndrome.

Search strategy and selection criteria

We searched MEDLINE for reports of studies published on or before Dec 14, 2015, using the terms "tricuspid valve", "tricuspid regurgitation", or "tricuspid stenosis". The studies were selected according to the objectives of the Review, including tricuspid valve anatomy and pathophysiology, natural history of tricuspid valve disease, and surgical and transcatheter treatment of tricuspid valve disease.

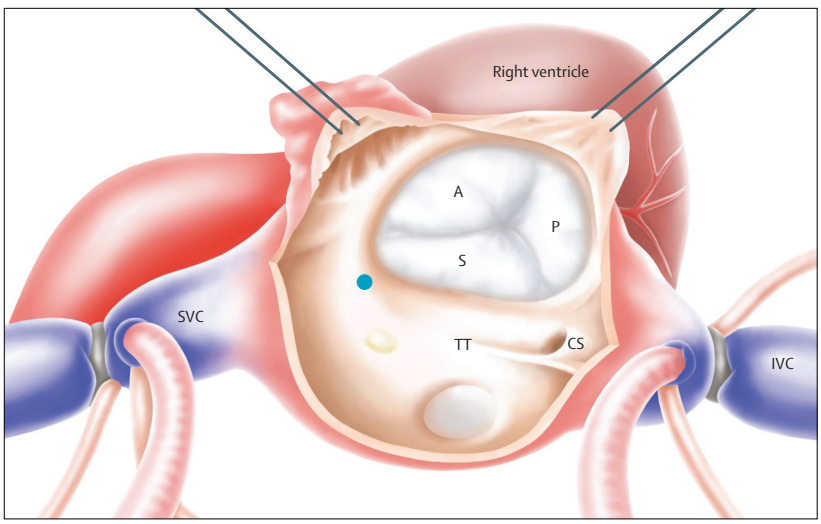

***Figure 1*: Anatomy of the tricuspid valve (surgical view through a right atriotomy)**
The blue spot indicates the position of the atrioventricular node, at the apex of the triangle of Koch. A=anterior leaflet. CS=coronary sinus. IVC=inferior vena cava. P=posterior leaflet. S=septal leaflet. SVC=superior vena cava. TT=tendon of Todaro. Adapted from Taramasso and colleagues,[4] by permission of Oxford University Press.

Tricuspid regurgitation

Aetiology

Moderate or severe tricuspid regurgitation has been estimated to be present in up to 1·6 million individuals in the USA.[6] The major causes of tricuspid regurgitation are listed in the panel. More than 80% of tricuspid regurgitation encountered in clinical practice is secondary (functional) in nature and related to tricuspid annular dilatation and leaflet tethering in the setting of right ventricular remodelling caused by pressure or volume overload (or both), myocardial infarction, or trauma. Among the main causes of tricuspid regurgitation are left-sided valvular (mitral > aortic) and myocardial diseases, often in association with raised pulmonary artery pressures. The prevalence of tricuspid regurgitation or tricuspid annular dilatation, or both, in patients undergoing surgery for mitral regurgitation has ranged from 8% to 65% across several studies.[7–11] There has been increasing appreciation of the effects of atrial fibrillation and right ventricular pacing on the emergence of tricuspid regurgitation.[12] With onset of atrial fibrillation, many older patients (aged >75 years) develop clinically significant degrees of tricuspid regurgitation, often in association with abnormalities of right ventricular compliance; restoration of sinus rhythm in this setting can lead to a marked reduction in tricuspid regurgitation severity. Tricuspid regurgitation with right ventricular pacing might result from intra-annular lead placement, leaflet trauma, or dyssynchrony.

Primary tricuspid regurgitation occurs as a consequence of congenital or acquired disease processes that affect the leaflets or chordal structures, or both. Rheumatic tricuspid valve disease is usually mixed in nature (ie, with elements of tricuspid regurgitation and tricuspid stenosis) and always occurs in association with concomitant mitral valve involvement. The cause of tricuspid regurgitation in an individual patient is established by integration of the clinical and echocardiographic findings.

***Panel:* Causes of tricuspid regurgitation**

Primary tricuspid regurgitation: diseases of the tricuspid valve leaflets or chordal structures, or both

Congenital disease
- Ebstein's anomaly
- Tricuspid valve dysplasia, hypoplasia, or cleft
- Double orifice tricuspid valve

Acquired disease
- Endocarditis
- Rheumatic disease (with left-sided disease)
- Carcinoid, serotonin-active drugs
- Tricuspid valve prolapse, flail
- Radiation
- Cardiac device (PPM, ICD) leads
- Trauma
  - Right ventricular endomyocardial biopsy
  - Blunt chest wall trauma
- Degenerated bioprosthesis

Secondary tricuspid regurgitation: diseases affecting the right ventricle and tricuspid annulus
- Right ventricular and tricuspid annular dilatation
  - Left-sided valvular and/or myocardial disease
  - Pulmonary hypertension independent of left-sided cardiac pathology
  - Right ventricular infarction with remodelling
- Chronic right ventricular pacing (dyssynchrony)
- Atrial fibrillation

ICD=implantable cardioverter-defibrillator. PPM=permanent pacemaker.

Assessment

Tricuspid regurgitation is observed far more often on echocardiography than it is acknowledged at the bedside. Indeed, it might not be recognised clinically until fairly late in its natural history. Tricuspid regurgitation is often first recognised on inspection of the jugular venous waveform with discernment of systolic "cv" waves. The murmur of tricuspid regurgitation is heard in relatively few patients. It is classically high pitched, holosystolic in timing, heard at the lower left sternal border, and louder during inspiration. A pulsatile, enlarged liver is a late finding, as are ascites and lower extremity oedema. Right ventricular systolic function is usually impaired when such signs of right heart failure are present.

The diagnosis of tricuspid regurgitation is most often made with transthoracic echocardiography (TTE), by which the cause and severity of the disorder can be established, the dimensions of the tricuspid annulus can be measured, right atrial and pulmonary artery pressures can be estimated, right ventricular function can be

assessed, and any associated left-sided valvular or myocardial disease can be defined. These findings are crucial to the development of an appropriate management strategy. Trace or mild degrees of tricuspid regurgitation of no clinical consequence can be seen in patients with normal tricuspid valve leaflets and annular dimensions. There is a linear relation between tricuspid valve annulus diameter and regurgitant volume. A diameter of 40 mm or more (or ≥21 mm/m²) is deemed clinically significant and has been used as a threshold at and beyond which repair is regarded as reasonable at the time of left-sided valve surgery.[2,3,8,13] The European Society of Echocardiography and the American Society of Echocardiography have provided specific recommendations for grading the severity of tricuspid regurgitation on the basis of a combination of qualitative, semiquantitative, and quantitative echocardiographic measures (table 1).[14–16] An example of severe tricuspid regurgitation is shown in figure 2.

Transoesophageal echocardiography (TEE) can be considered when TTE images are inadequate, although visualisation of the anteriorly located tricuspid valve can also be difficult with this technique. The accurate assessment of right ventricular systolic function is challenged by geometric and image acquisition constraints, as well as by dynamic changes in right ventricular loading conditions. Echocardiography using colour Doppler tissue imaging, speckle tracking, and real-time three-dimensional techniques, as well as cardiac magnetic resonance (CMR) imaging, can provide more accurate quantification of right ventricular function and tricuspid regurgitation severity.[17–22] Three-dimensional echocardiography can also provide a more accurate depiction of leaflet anatomy and annular dimensions than standard two-dimensional techniques. Whereas CMR is not widely available and often contraindicated by the presence of indwelling device leads or inability of the patient to tolerate the magnet, automated advanced TTE imaging of the right ventricle and tricuspid valve is becoming more widespread. CT, which is useful for precise measurements of the tricuspid annulus and depiction of surrounding tricuspid valve structures,[23,24] has assumed increasing importance in planning transcatheter interventions. The use of right heart catheterisation to assess the severity of tricuspid regurgitation has decreased over time. Ventricularisation of the right atrial waveform indicates severe tricuspid regurgitation. Direct measurement of pulmonary artery pressures and resistance can be helpful in the assessment and management of selected patients with pulmonary hypertension.

	Mild	Moderate	Severe
Qualitative measures			
Tricuspid valve morphology	Normal or abnormal	Normal or abnormal	Abnormal, flail, or large coaptation defect
Colour flow jet*	Small, central	Intermediate	Large central jet or eccentric wall impinging jet
Continuous wave signal of TR jet	Faint, parabolic	Dense, parabolic	Dense, triangular with early peaking (peak <2 m/s in massive TR)†
Semiquantitative measures			
Vena contracta width (mm)*	Not defined	<7	≥7
PISA radius (mm)‡	≤5	6–9	>9
Hepatic vein flow§	Systolic dominance	Systolic blunting	Systolic flow reversal
Tricuspid inflow	Normal	Normal	E-wave dominant (≥1 cm/s)
Quantitative measures			
EROA (mm²)	Not defined	Not defined	≥40
Regurgitant volume (mL/beat)	Not defined	Not defined	≥45
Right atrial/right ventricular/IVC dimension¶	..	..	..

TR=tricuspid regurgitation. PISA=proximal isovelocity surface area. EROA=effective regurgitant orifice area. IVC=inferior vena cava. *At a Nyquist limit of 50–60 cm/s. †In the absence of other causes of raised right atrial pressures. ‡Baseline Nyquist limit shift of 28 cm/s. §Unless other reasons of systolic blunting (atrial fibrillation, raised right atrial pressure). ¶Unless for other reasons, the sizes of the right atrium, right ventricle, and IVC are usually normal in patients with mild TR. An end-systolic right ventricular eccentricity index >2 is in favour of severe TR. In acute severe TR, the right ventricular size is often normal. In chronic severe TR, the right ventricle is classically dilated. Accepted cutoff values for non-significant right-sided chamber enlargement (measurements obtained from the apical four-chamber view): mid-right ventricular dimension ≤33 mm, right ventricular end-diastolic area ≤28cm², right ventricular end-systolic area ≤16 cm², right ventricular fractional area change >32%, maximal right atrial volume ≤33 mL/m². An IVC diameter <1·5 cm is regarded as normal. Reproduced from Lancellotti and colleagues,[14] by permission of Oxford University Press.

Table 1: **Echocardiographic grading of tricuspid regurgitation severity**

Prognosis

The adverse effects of tricuspid regurgitation on long-term outcomes have been reported for several cohorts of patients. In a study of 5223 ambulatory patients in the US Veteran's Health Administration system who were followed up for 4 years, increasing severity of tricuspid regurgitation was associated with worse survival, independent of age, biventricular systolic function, right ventricular size, and inferior vena cava dilatation.[1] 5-year survival was 74% in 813 medically managed patients with moderate or severe, isolated tricuspid regurgitation followed up at a single centre in South Korea.[25] Tricuspid regurgitation has been independently associated with reduced long-term survival in patients with ischaemic or idiopathic left ventricular systolic dysfunction, with or without clinical heart failure.[26–28] The effect of significant tricuspid regurgitation on outcomes in patients with severe aortic stenosis referred for transcatheter aortic valve replacement (TAVR) is uncertain, because few data are available.[29] However, in patients with low-flow, low-gradient, severe aortic stenosis and reduced left ventricular systolic function, moderate or severe tricuspid regurgitation is independently associated with increased risks of total and cardiovascular mortality, irrespective of the treatment used (surgical aortic valve replacement [SAVR], TAVR, or conservative therapy).[30]

Pharmacological therapy for tricuspid regurgitation is restricted to the use of diuretics for systemic congestion in the late phases of the disease, the selective use of pulmonary vasodilators in patients with pulmonary artery hypertension independent of left-sided heart

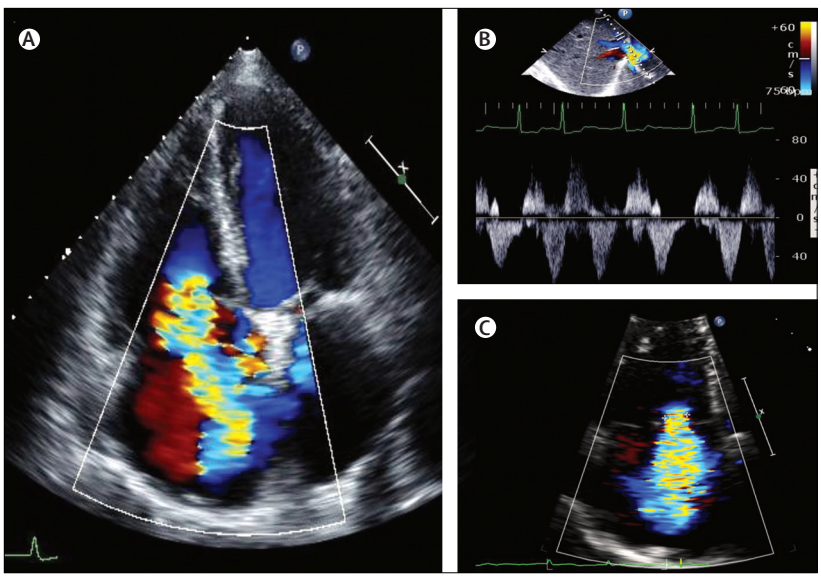

Figure 2: **Doppler echocardiography images indicative of severe tricuspid regurgitation**
(A) Large central colour jet of tricuspid regurgitation appears yellow-blue (four-chamber view). (B) Hepatic vein systolic flow reversal (inferior vena cava). Note the positive Doppler velocity signal immediately after the QRS complex indicating systolic flow into the hepatic veins. (C) Vena contracta width more than 7 mm. Measurement is made at the "neck" of the tricuspid regurgitation jet at the level of the tricuspid valve.

disease, and the management of atrial fibrillation. Such interventions are symptom and quality of life specific and do not affect survival.

Tricuspid stenosis

The causes of native valve tricuspid stenosis are limited to congenital defects, rheumatic heart disease, and obstructing right atrial masses, such as prolapsing myxoma. Xenograft or mechanical prosthetic valve dysfunction can also result in obstruction, including from thrombosis. The natural history of rheumatic tricuspid stenosis, which most often coexists with tricuspid regurgitation, is dominated by that caused by mitral or aortic valve involvement; surgical correction is sometimes required at the time of left-sided valve operations. Tricuspid valve balloon valvuloplasty has limited efficacy.[2,3] Fibrinolytic therapy for prosthetic tricuspid valve thrombosis is usually regarded as first-line therapy.[2,3]

Surgical treatment of tricuspid regurgitation

Current recommendations

Isolated primary tricuspid valve surgery

Current recommendations for surgery are shown in table 2.[2,3] Expert opinion holds that tricuspid valve surgery is reasonable for patients with symptoms of severe primary tricuspid regurgitation that are unresponsive to pharmacological treatment. Tricuspid valve surgery can also be selectively considered for asymptomatic or minimally symptomatic patients with progressive degrees of right ventricular dysfunction and preferably before onset of right heart failure.[2,3] Isolated primary tricuspid valve surgery is usually done via a right minithoracotomy approach, using cardiopulmonary bypass with peripheral bicaval cannulation. It can be performed on the beating heart. The outcomes of isolated primary tricuspid valve surgery are not well established, because few reports are available in the scientific literature. Different series report a primary tricuspid valve repair rate of about 70%, with perioperative mortality rates ranging between 4% and 17%. Factors associated with increased risk of mortality are age, New York Heart Association class, right ventricular failure, and pulmonary hypertension.[31–35] There is a paucity of robust comparisons of primary tricuspid valve repair versus replacement.

Tricuspid valve surgery at the time of left-sided heart valve surgery

Severe tricuspid regurgitation of either a primary or secondary nature does not predictably improve after left-sided valve surgery, even with correction of any associated pulmonary hypertension, and should be addressed at the time of the index operation directed at left-sided valve disease.[2,3] There is greater variability in the surgical approach to mild or moderate tricuspid regurgitation at the time of left-sided valve surgery, related in part to widely differing estimates of the incidence and risk of residual or progressive postoperative tricuspid regurgitation, heart failure, and death when tricuspid regurgitation is not addressed.[36,37] Risk factors for persistent or worsening tricuspid regurgitation after mitral valve operation identified in observational studies include tricuspid annular dilatation 40 mm or more, extent of tricuspid valve leaflet tethering, pulmonary artery pressure, atrial fibrillation, non-myxomatous cause of mitral valve disease, and intra-annular positioning of cardiac device leads.[8,38] Because of the hazards associated with reoperation, concomitant tricuspid valve repair is deemed reasonable for patients with mild or moderate tricuspid regurgitation and clinically significant annular dilatation (>40 mm) or a history of right heart failure.[2,3] Several observational studies and one RCT have reported improved echocardiographic and functional outcomes after tricuspid valve repair in this context, without an increase in operative risk, although a long-term survival benefit has not been definitively established.[10,11,39–42]

According to the Society for Thoracic Surgeons database, among 46 500 isolated primary mitral valve operations done in the USA between 2011 and 2014, tricuspid valve repair was undertaken in 4% of patients with none or mild tricuspid regurgitation, 35% of patients with moderate tricuspid regurgitation, and 79% of patients with severe tricuspid regurgitation (Gammie J, University of Maryland, personal communication). The variability in the approach to moderate tricuspid regurgitation at the time of mitral valve surgery reflects uncertainty regarding the benefits of repair; however, its

hazards are regarded by most experts to be trivial. A Cardiothoracic Surgery Network RCT to investigate the efficacy and safety of tricuspid valve repair in 400 patients with either moderate tricuspid regurgitation or less than moderate tricuspid regurgitation and tricuspid annular dilatation of 40 mm or more undergoing mitral valve surgery will launch in the USA, Canada, and Germany in 2016 (NCT number pending).

Isolated, reoperative tricuspid valve surgery late after previous left-sided heart valve surgery

Late, secondary tricuspid regurgitation occurring after previous left-sided heart valve surgery represents a particular clinical and surgical challenge. In most cases, late, severe secondary tricuspid regurgitation is a consequence of the continued progression of initially mild or moderate tricuspid regurgitation, especially in patients with dilated tricuspid annuli. In this group of patients, tricuspid surgery is often associated with high morbidity and mortality (up to 25%)[43–45] because of the presence of variable degrees of right ventricular dysfunction and pulmonary vascular disease; lower rates of adverse outcomes have been reported in recent surgical series.[46,47] Optimum surgical technique (eg, repair *vs* replacement, access, type of prosthesis) and timing remain controversial.

Tricuspid valve surgery can be considered late after left-sided valve surgery in select, symptomatic patients with severe tricuspid regurgitation in the absence of severe right ventricular dysfunction or pulmonary hypertension.[2,3] Reoperative tricuspid valve surgery is associated with poor outcomes in patients with severe right heart failure and organ dysfunction.[6,45] When performed earlier in the natural history of the disease, improved results with acceptable perioperative mortality (5–6%) are possible.[48] Multidisciplinary pre-procedural assessment and risk stratification are crucial to the identification of patients who are unlikely to survive or derive meaningful functional benefit after reoperation.

	Class of recommendation	Level of evidence
AHA and ACC (2014)[3]		
Primary TR		
Severe TR at the time of left-sided valve surgery	I	C
Symptoms caused by severe TR not responsive to medical therapy	IIa	C
Asymptomatic or minimally symptomatic severe TR and progressive right ventricular dilatation and/or dysfunction	IIb	C
Secondary TR		
Severe TR at the time of left-sided valve surgery	I	C
Mild, moderate, or greater TR at the time of left-sided valve surgery with either a dilated annulus (≥40 mm or ≥21 mm/m^2) or evidence of previous right heart failure	IIa	B
Moderate TR and pulmonary hypertension at the time of left-sided valve surgery	IIb	C
Reoperation for persistent symptoms caused by isolated severe TR after previous left-sided valve surgery in absence of severe pulmonary artery hypertension or right ventricular dysfunction	IIb	C
ESC and EACTS (2012)[2]		
Primary TR		
Severe TR at the time of left-sided valve surgery	I	C
Severe symptomatic isolated TR without severe right ventricular dysfunction	I	C
Moderate TR at the time of left-sided valve surgery	IIa	C
Asymptomatic or mildly symptomatic isolated severe TR and progressive right ventricular dilatation or deterioration of right ventricular function	IIa	C
Secondary TR		
Severe TR at the time of left-sided valve surgery	I	C
Mild or moderate TR with dilated annulus (≥40 mm or >21 mm/m^2) at the time of left-sided valve surgery	IIa	C
Severe TR late after left-sided valve surgery with symptoms or progressive right ventricular dilatation or dysfunction, in the absence of left-sided valve dysfunction, severe right or left ventricular dysfunction, and severe pulmonary vascular disease	IIa	C

Class of recommendation: I: benefit>>>risk; procedure should be done; usefulness or efficacy established; IIa: benefit>>risk; additional studies with focused objectives required; it is reasonable to do procedure; evidence favours usefulness or efficacy; IIb: benefit>risk; additional studies with broad objectives needed; procedure may be considered; usefulness or efficacy less well established. Level of evidence: B: limited populations evaluated; data derived from a single randomised trial or non-randomised studies; C: very limited populations studied; only consensus opinion of experts, case studies, standard of care. AHA=American Heart Association. ACC=American College of Cardiology. TR=tricuspid regurgitation. ESC=European Society of Cardiology. EACTS=European Association of Cardiothoracic Surgery.

***Table 2*: Guidelines for the surgical management of tricuspid regurgitation**

Surgical considerations

Overview of strategies

Surgical strategies vary according to surgeon preference and institutional expertise. Tricuspid valve surgery at the time of left-sided valve surgery is usually done via a median sternotomy or minimally invasive minithoracotomy approach. Isolated tricuspid valve surgery, however, can be performed on the beating heart with cardiopulmonary bypass, either through a median sternotomy or a right anterolateral thoracotomy. The latter approach might reduce the risk of accidental cardiac or graft injury during reoperation.[49]

The cause and mechanism of valve dysfunction determine whether valve repair or replacement should be done. With complex lesions causing primary tricuspid regurgitation, or in the case of severe tricuspid stenosis, reparability depends greatly on the skill of the surgeon. The reconstruction technique is usually tailored to the anatomy. Long-term results of tricuspid repair for primary tricuspid regurgitation are largely unknown and tricuspid valve replacement might be preferred in most cases of complex, primary tricuspid regurgitation (eg, carcinoid disease).[50]

The principles of surgical therapy for secondary tricuspid regurgitation include elimination of increased right ventricular afterload (eg, by correction of left-sided valve disease) and correction of tricuspid annular dilatation usually by means of an annuloplasty procedure. When severe tricuspid valve tethering is also present (as often seen in late-onset tricuspid regurgitation after

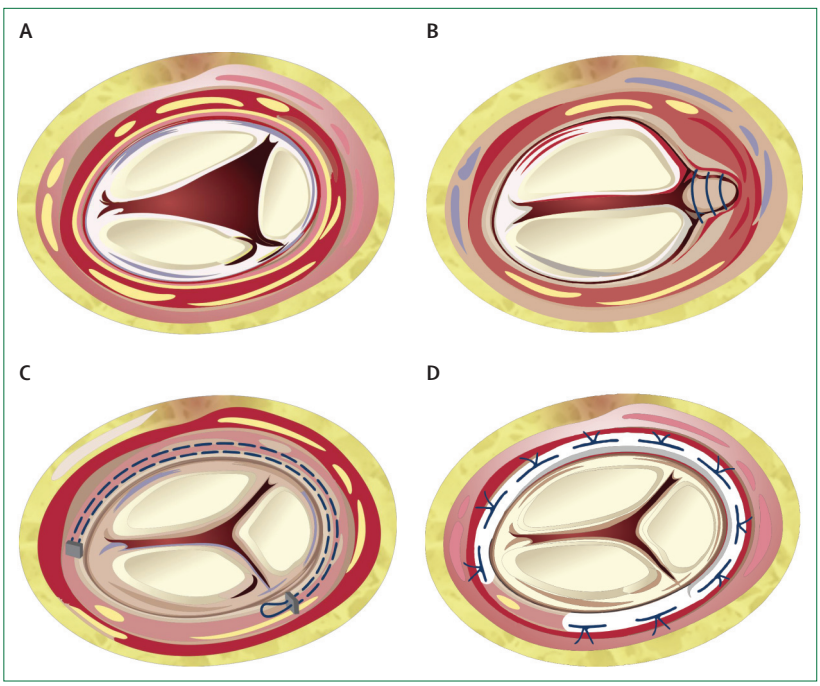

***Figure 3*: Tricuspid annuloplasty repair techniques**
(A) Tricuspid valve before surgical intervention. (B) Surgical plication of the posterior leaflet (Kay bicuspidisation repair). (C) De Vega suture repair, which allows reduction of the annular area and increases leaflet coaptation. (D) Ring annuloplasty with use of an incomplete semirigid prosthetic ring.

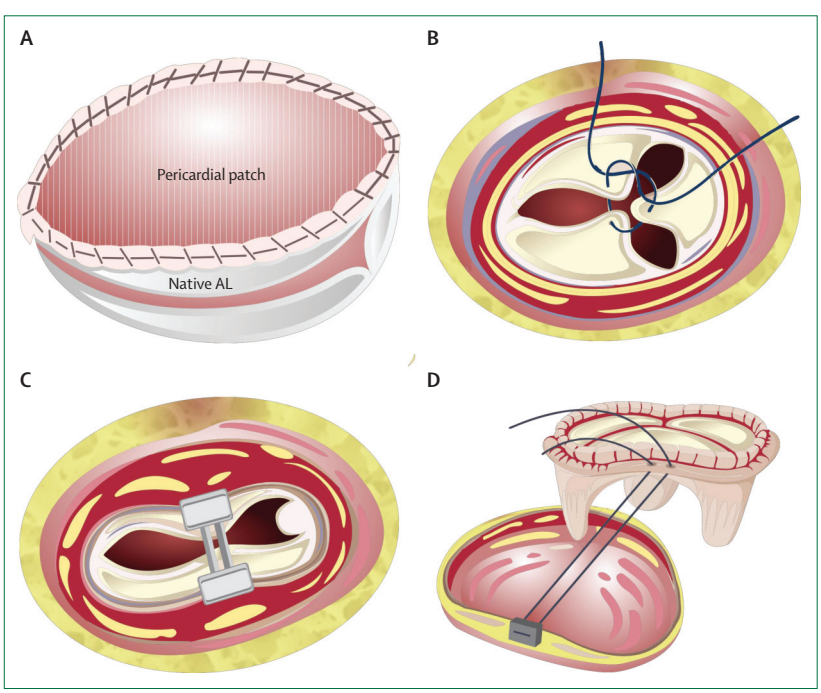

***Figure 4*: Adjunctive repair and valve replacement techniques for tricuspid valve disease**
(A) Anterior leaflet (AL) augmentation with pericardial patch. (B) "Clover" repair. (C) Double orifice technique. (D) Tricuspid valve replacement with bioprostheses.

left-sided valve surgery), the use of adjunctive surgical techniques or tricuspid valve replacement should be considered.[13]

Tricuspid valve repair

Tricuspid annuloplasty is the foundation of surgical therapy for secondary (functional) tricuspid regurgitation and is intended to improve leaflet coaptation by correcting annular dilatation and restoring annular geometry. The two principal surgical methods used to perform tricuspid annuloplasty involve suture and ring annuloplasty techniques (figure 3). Suture annuloplasty methods reduce the size of the tricuspid annulus with a continuous suture to cinch the annulus. Most suture annuloplasty techniques are modified versions of the Kay bicuspidisation[51] or De Vega repair[52] and consist of the plication of both the posterior and anterior portions of the annulus (figure 3). The main advantages of suture annuloplasty techniques are that they are technically easy and can be done quickly. Moreover, compared with ring annuloplasty, a prosthetic implant is not used with suture annuloplasty and the risk of postoperative conduction disturbances is lower.

With ring annuloplasty, the size of the tricuspid annulus is permanently fixed by implantation of a rigid or semirigid prosthetic, undersized ring. Compared with the use of flexible annuloplasty bands, implantation of a rigid or semirigid ring is associated with a reduced incidence of late, recurrent tricuspid regurgitation and is regarded as the standard for surgical repair.[53,54] With flexible rings, however, there is a reduced risk of ring dehiscence or fracture.[55,56]

The goal of tricuspid annuloplasty is to prevent further annular dilatation while preserving leaflet mobility and promoting a large surface of coaptation. There are several specifically shaped tricuspid prosthetic rings available to fit the non-planar three-dimensional configuration of the native tricuspid annulus.[57–59] Tricuspid annuloplasty rings are incomplete, to preserve the native annulus at the level of the atrioventricular node and reduce the risk of postoperative heart block (figure 3).

Both the durability of tricuspid valve repair and clinical outcomes have been improved with the use of annuloplasty rings.[42] The proportion of patients with recurrent moderate or severe tricuspid regurgitation 5 years after surgery is about 10% for those treated with ring annuloplasty compared with 20–35% for those treated with suture repair.[8,41,54,60] A meta-analysis of 13 trials has shown that the proportion of patients with recurrent, clinically significant tricuspid regurgitation at 15 years was significantly higher in those who underwent suture annuloplasty than in those who underwent ring annuloplasty (50·5% [SD 5·9] with ring annuloplasty *vs* 78·9% [5·0] with suture annuloplasty; p=0·0107).[61] Survival at 15 years, however, does not seem to differ significantly between the two surgical approaches (48·0% [4·6] with ring annuloplasty *vs* 34·6% [4·7] with suture annuloplasty; p=0·441).

Factors associated with failed annuloplasty repair include marked leaflet tethering (coaptation height >1 cm and tenting volume >2·3 mL), atrial fibrillation, greater

tricuspid regurgitation severity, higher pulmonary artery pressures, larger annular size, concomitant mitral valve replacement rather than repair, worse left ventricular function, and the presence of intra-annular pacemaker leads.[54,60,62–67]

Adjunctive repair techniques

Adjunctive repair techniques might be necessary to augment the effects of ring annuloplasty in patients with marked leaflet tethering and right ventricular remodelling. Anterior leaflet augmentation with the use of an autologous pericardial patch can improve leaflet coaptation while maintaining leaflet mobility (figure 4).[68] The "clover" technique approximates the free edges of the three leaflets, producing a clover-shaped valve (figure 4).[69] This technique has also been used to treat selected patients with complex primary tricuspid regurgitation.[70] Promising outcomes have been reported with the double orifice valve technique,[71] which is done by passing two sutures from the middle of the anterior portion of the annulus to the septal portion of the annulus, forcing leaflet coaptation (figure 4). Long-term outcomes and durability of these adjunctive techniques are not yet well established.

Tricuspid valve replacement

Tricuspid valve replacement (figure 4) is undertaken when valve repair is not technically feasible or predictably durable. In many patients with secondary tricuspid regurgitation and marked right ventricular remodelling and leaflet tethering, as well as in patients with complex primary tricuspid regurgitation or severe tricuspid stenosis, valve replacement should be regarded as the first option. Although bioprostheses are currently favoured,[72] no differences in survival or adverse events at long-term follow-up have been recorded in patients receiving mechanical or biological valves.[73–75] The choice of prosthesis type should be individualised according to the clinical context, operative findings, and patient preferences.[2,3] Long-term anticoagulation might be a challenge in patients with a history of injection drug use and tricuspid valve endocarditis. Management of right ventricular pacing and defibrillator leads after tricuspid valve replacement is challenging and might require epicardial placement or extra-annular tunnelling.

Transcatheter therapies for tricuspid regurgitation

Challenges for less invasive techniques

Because the risks of isolated tricuspid valve surgery are substantial, particularly in the context of reoperation late after left-sided valve surgery,[43–45] there is keen interest in the development of less invasive percutaneous transcatheter techniques for treating severe tricuspid

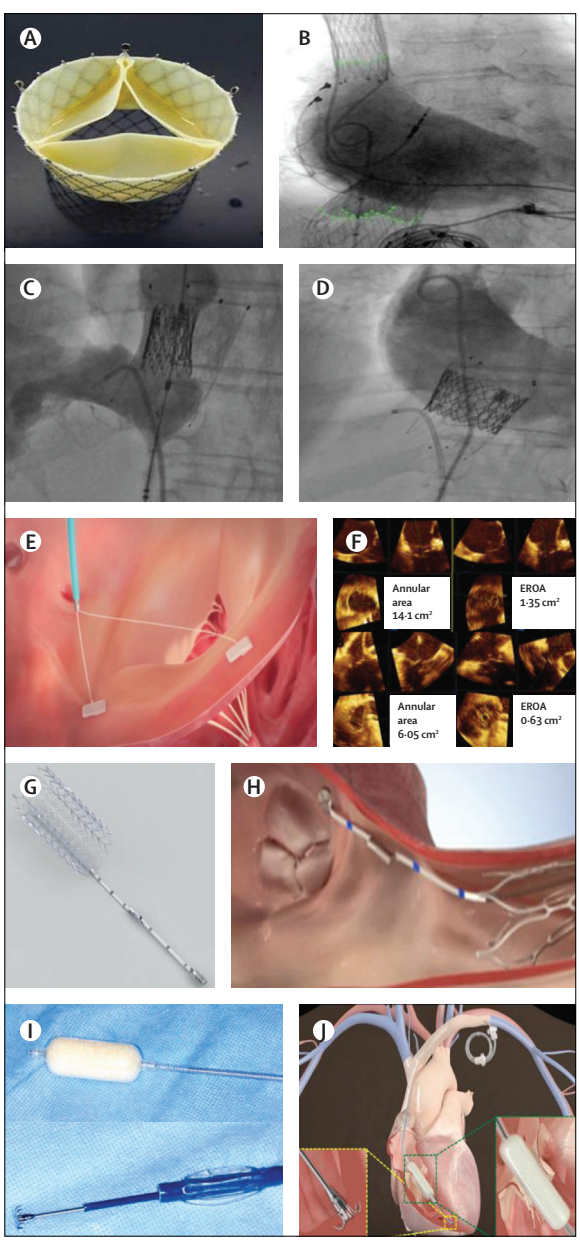

***Figure 5*: Transcatheter therapies for severe tricuspid regurgitation[76]**
(A–B) TricValve device. (A) Three leaflets of bovine pericardium mounted on a self-expandable nitinol stent. (B) Right atrial angiography following heterotopic TricValve implants at the level of superior and inferior cavoatrial junctions. No leaks are observed. (C–D) Balloon-expandable valve. (C) Implant of a peripheral stent at the level of the inferior cavoatrial junction to create a landing zone for the implant of a balloon-expandable transcatheter valve. (D) Right atrial angiography following transcatheter implantation of a 29 mm SAPIEN XT valve at the inferior atriocaval junction. No reflux of contrast dye into the inferior vena cava is observed. (E–F) Mitralign device. (E) Pledgets delivered at the anterior-posterior and septal-posterior tricuspid commissures. (F) Three-dimensional transoesophageal echocardiographic assessment at baseline (left) and following successful Mitralign implant (right). (G–H) TriCinch device. (G) The device consists of a corkscrew anchor, a self-expanding stent, and a Dacron band connecting both. (H) The corkscrew anchor is fixed into the anterior-posterior tricuspid valve annulus and the stent implanted into the inferior vena cava. Tension is applied to the system through the connecting Dacron band leading to a reduction in septal-lateral tricuspid annulus dimension. (I–J) FORMA Repair System. (I) The device consists of a foam-filled balloon (spacer) and an anchoring system. (J) The anchoring system is fixed at the apex of the right ventricle and the spacer is positioned at the level of the tricuspid leaflets to improve valve leaflet coaptation. EROA=effective regurgitant orifice area.

regurgitation. However, the development of such techniques must overcome several major anatomical challenges: large tricuspid annulus dimensions (usually >40 mm in diameter) with a non-planar and elliptical shape; absence of calcium; right ventricular morphology (trabeculations, muscle bands, thin apical wall); and proximity of other structures, such as the coronary sinus, atrioventricular node and bundle of His, vena cavae, right coronary artery, and right ventricular outflow tract. Because of such challenges, transcatheter tricuspid valve replacement has not yet been performed in man. As an alternative to valve replacement, three types of transcatheter therapies have recently emerged for treating severe tricuspid regurgitation: heterotopic implant of a transcatheter valve at the level of the vena cava; devices dedicated to reduce tricuspid annular dimensions (transcatheter tricuspid annuloplasty devices); and devices dedicated to improve tricuspid valve leaflet coaptation.

Heterotopic caval transcatheter valve implantation

The objective of heterotopic caval transcatheter valve implantation is to reduce the reflux of severe tricuspid regurgitation into the vena cavae and thereby improve symptoms and signs of right heart failure, albeit without affecting the magnitude of tricuspid regurgitation. The large and variable diameters of superior and inferior vena cavae and the length of the landing zone between the hepatic veins and inferior cavo–right atrial junction are major challenges. Two valve prototypes, the self-expandable TricValve (P+F Products + Features Vertriebs GmbH, Vienna, Austria in cooperation with Braile Biomedica, São José do Rio Preto, Brazil) and the balloon-expandable Edwards valve (Edwards Lifesciences, Irvine, CA, USA), have been tested in proof-of-concept trials for this purpose.

The TricValve consists of a self-expandable nitinol frame and three leaflets of bovine pericardium (figure 5), with sizes from 28 to 43 mm. The valves are implanted through a transvenous approach at the superior and inferior cavoatrial junctions. TricValve implantation has been attempted in five patients deemed to be at prohibitive risk for surgery.[76–78] Procedural success was obtained in four of the patients, and one patient died by 30 days of follow-up. Early improvement in heart failure symptoms was noted in two patients, but four of the five patients had died by 7 months' mean follow-up, mainly related to severe non-cardiac comorbidities.

Heterotopic caval implantation of 29 mm balloon-expandable Edwards SAPIEN XT or SAPIEN 3 valves, currently approved for TAVR procedures, has been performed off-label for patients with inoperable chronic severe tricuspid regurgitation. In these cases, a large self-expandable peripheral stent was implanted at the cavoatrial level before valve implant to create a landing zone to facilitate transcatheter valve anchoring (figure 5). Ten patients have been treated under a compassionate clinical use programme.[76,79] The implant was limited to the inferior cavoatrial junction in nine patients; one patient received dual valve implants at the superior and inferior cavoatrial junction. Successful valve implantation with no periprocedural complications was achieved in all patients with no residual transvalvular or paravalvular leaks (figure 5). Early post-implant improvements in right heart failure were reported in eight of nine patients. However, mortality at a mean follow-up of 9 months was very high (90%), caused by either terminal heart failure or non-cardiac comorbidities.

Clearly, further studies are needed to investigate the safety and efficacy of this strategy for the reduction of the manifestations of right heart failure with severe tricuspid regurgitation. These studies should also account for the persistence of right atrial and right ventricular volume overload in the context of untreated severe tricuspid regurgitation, as well as the long-term adverse consequences of the "ventricularisation" of right atrial pressure. The next steps for the clinical development of heterotopic caval valve implants are summarised in table 3.

Transcatheter tricuspid valve annuloplasty

Significant tricuspid annular dilatation is the main mechanism underlying severe secondary (functional) tricuspid regurgitation. Surgical ring annuloplasty is the procedure of first choice in the treatment of secondary tricuspid regurgitation. Transcatheter tricuspid annuloplasty has been done with the Mitralign (Mitralign Inc, Tewksbury, MA, USA) and TriCinch (4Tech Cardio Ltd, Galway, Ireland) devices.

The Mitralign device mimics the Kay surgical procedure,[51] which consists of the plication of the anterior and posterior portions of the tricuspid annulus resulting in a functionally bicuspid valve. The device consists of two pairs of pledgets implanted at the anterior-posterior and septal-posterior commissures and connected by a suture (figure 5). Once implanted, the two pledgeted sutures are brought together with plication of the annulus. Initial experience with this device has been reported, with demonstration of the feasibility of the procedure and a substantial reduction in tricuspid annular dimension and effective orifice regurgitation area.[80] The safety and feasibility of this device for treating severe tricuspid regurgitation are being investigated in a prospective registry study (table 3).

The TriCinch device consists of a corkscrew anchor implanted into the anterior-posterior tricuspid annulus and a self-expanding stent implanted in the inferior vena cava.[81] The annulus anchor and the inferior vena cava stent are connected via a Dacron band (figure 5). A reduction in tricuspid annular dimensions is achieved by applying tension with the Dacron band. The PREVENT registry study is currently assessing the safety and potential efficacy of this device (table 3).

 Published online April 2, 2016 http://dx.doi.org/10.1016/S0140-6736(16)00740-6

	Device	Study design	Number of participants	Primary endpoints
HOVER (NCT02339974)	Edwards SAPIEN XT (heterotopic caval implant)	Prospective registry	30	Procedural success at 30 days, defined as device success and no device or procedure-related serious adverse events including all death, all stroke, myocardial infarction, acute kidney injury grade 3, life-threatening bleeding, major vascular complications (arterial or venous—requiring unplanned intervention), pericardial effusion or tamponade requiring drainage, vena cava syndrome. Individual success at 1 year, defined as device success and no readmissions to hospital for right-sided heart failure or right-sided heart failure equivalents including drainage of ascites or pleural effusions, new listing for heart transplant, VAD, or other mechanical support; and KCCQ improvement >10 *vs* baseline and 6MWT improvement >50 m *vs* baseline
TRICAVAL (NCT02387697)	Edwards SAPIEN XT (heterotopic caval implant)	Randomised, open-label	40	Maximum relative VO_2 uptake at 3 months (difference of means in maximum relative VO_2 uptake at 3 months compared with control group)
SCOUT (NCT02574650)	Mitralign	Prospective registry	15	Technical success at 30 days defined as freedom from death with successful access, delivery, and retrieval of the device delivery system, and deployment and correct positioning of the intended device(s), and no need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure
PREVENT (NCT02098200)	TriCinch	Prospective registry	24	Safety: percentage of participants with major adverse events within 30 days of the procedure, including death, Q-wave myocardial infarction, cardiac tamponade, cardiac surgery for failed TriCinch implantation, stroke, or septicaemia. Efficacy: reduction in the degree of tricuspid regurgitation measured immediately after the procedure at discharge compared with baseline; ability to reduce tricuspid regurgitation by at least 1 degree immediately following implantation of the TriCinch device assessed by means of quantitative echocardiographic parameters
Early Feasibility Study of the Edwards Tricuspid Transcatheter Repair System (NCT02471807)	FORMA	Prospective registry	15	Procedural success defined as device success and freedom from device or procedure-related serious adverse events at 30 days

VAD=ventricular assist device. KCCQ=Kansas City Cardiomyopathy Questionnaire. 6MWT=6 min walk test. VO_2=oxygen consumption.

***Table* 3: Ongoing and future studies on transcatheter therapies for treating severe tricuspid regurgitation**

Coaptation device

The FORMA device (Edwards Lifesciences) is designed to reduce the severity of tricuspid regurgitation by improving leaflet coaptation. The device consists of a spacer (foam-filled balloon) that is advanced along a rail anchored at the right ventricular apex (figure 5). The device is implanted through a venous axillary-subclavian approach. Clinical and echocardiographic results from the first seven patients treated with this device have been reported.[82] The device was successfully implanted in all patients with no periprocedural complications. The severity of tricuspid regurgitation was reduced by one grade (from severe to moderate) in all patients and was associated with improvements in functional status and a reduction in peripheral oedema at 30 days. Further feasibility data will be obtained from a prospective registry study (table 3).

Transcatheter tricuspid valve replacement

Transcatheter tricuspid valve replacement with the use of a self-expandable valve system has been done successfully in the preclinical setting, but not in human beings.[83] As has been the case for treatment of left-side bioprosthetic valve dysfunction,[84] transcatheter valve replacement has been applied successfully to patients with tricuspid bioprosthetic valve dysfunction.[85,86] Future studies are needed to determine the mid-term to long-term outcomes of such procedures.

Edge-to-edge repair

The Mitraclip device (Abbott, Menlo Park, CA, USA) is a 4-mm-wide cobalt-chromium, polyester-covered implant with two arms that are opened and closed by control mechanisms on the clip delivery system. The Mitraclip system is a transcatheter alternative for the treatment of selected patients with mitral regurgitation. Recently, the first-in-human use of Mitraclip for the treatment of tricuspid regurgitation was reported. Three patients with severe secondary (functional) tricuspid regurgitation were successfully treated with no major complications and a reduction in severity of acute tricuspid regurgitation.[87,88] Further studies with longer follow-up are warranted.

Conclusions and future perspectives

Severe secondary tricuspid regurgitation should be addressed at the time of surgery for left-sided valve disease. Furthermore, there is growing consensus on the basis of observational data that moderate or lesser degrees of tricuspid regurgitation should also be managed at the

time of left-sided valve surgery with restrictive ring annuloplasty when tricuspid annular dilatation is present. This strategy will be studied prospectively in an RCT set to launch in 2016. The development of progressive tricuspid annular dilatation and worsening tricuspid regurgitation in the years following left-sided surgery is a challenging situation, especially in view of the increased morbidity and mortality associated with reoperative tricuspid valve surgery in older patients with a burden of comorbidities, biventricular dysfunction, and pulmonary vascular disease. Surgery for isolated, severe, primary tricuspid regurgitation also carries substantial risk and most often the need for valve replacement. There is a clinical need for less invasive therapies for treating severe tricuspid regurgitation. However, the anatomical features of the tricuspid valve apparatus and right heart chambers have made transcatheter treatment of the tricuspid valve very challenging. Several transcatheter therapies have recently emerged that are aimed to reduce caval reflux, shorten the dimensions of the tricuspid annulus, or improve leaflet coaptation. Few data on safety and feasibility are available. Transcatheter tricuspid valve replacement has not been attempted in man. Continued refinement of transcatheter techniques offers hope for the emergence of less invasive means to treat severe tricuspid regurgitation in many patients deemed at prohibitive or high surgical risk.

Contributors

JR-C, MT, and PTO'G participated in conception and design of the manuscript; data collection, analysis, and interpretation; drafting of the manuscript; and critical review of the manuscript for important intellectual content. All authors approved the final version of the submitted manuscript.

Declaration of interests

JR-C has received research grants from Edwards Lifesciences. MT and PTO'G declare no competing interests.

Acknowledgments

We thank Francesco Maisano for his mentorship and thoughtful review of the manuscript.

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