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Patients' selection for transcatheter tricuspid valve interventions: Who will benefit?

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ABSTRACT

Tricuspid regurgitation (TR) is a common valvular pathology and is associated with significant morbidity and mortality. However, there is no currently defined optimal management strategy: medical therapy is limited to diuretics, and tricuspid valve surgery is rarely performed and associated with high risks. This has led to the emergence of numerous transcatheter therapies that are showing promising early results but are faced with multiple challenges. The tricuspid valve anatomy is complex and variable, imaging of tricuspid valve by echocardiography can be difficult, and current grading of TR severity and right ventricular size and function is mostly subjective. Also, the optimal timing of the intervention and appropriate selection of patients who will benefit remain topics of debate with limited supporting data. In this review, we present the current challenges and considerations in patients' selection and propose a trial design and selection criteria aimed to address these limitations.

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Tricuspid regurgitation (TR) is a challenging valvular lesion as it poses an unmet clinical need. While it is quite common, with an estimated prevalence of >1.5 million people, and a yearly incidence of 200,000 patients in the United States,[1] isolated tricuspid valve (TV) surgery remains infrequent and among the highest risk valve surgeries, with an estimated in-patient mortality of 8.8%.[2] This has resulted in a large number of patients with untreated severe TR, which is associated with poor prognosis, in terms of morbidity and mortality.[3–5] In response to this clinical need, a number of transcatheter TV interventions (TTVI) have emerged recently and have shown promising results in their early feasibility trials.[6,7] However, a common key aspect to the success of such therapies is appropriate patient selection, which is a topic of active debate in both the interventional and surgical communities with no current accepted selection criteria to identify patients that would benefit from these technologies.

In this current report, we aim to present the challenges and the key considerations when considering patients for TTVI. These may be grouped into four categories: 1) Assessment of TR 2) Understanding

Abbreviations: AF, Atrial fibrillation; CMR, Cardiac magnetic resonance; EROA, Effective regurgitant orifice area; HF, Heart failure; NYHA, New York Heart Association; RV, Right ventricle or ventricular; SPAP, Systolic pulmonary artery hypertension; S-TDI, S wave tissue Doppler imaging; TA, Tricuspid annulus; TAPSE, Tricuspid annular plane systolic excursion; TR, Tricuspid regurgitation; TTVI, Transcatheter tricuspid valve intervention; TV, Tricuspid valve.

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the natural history of the disease, 3) Knowledge of currently available therapeutic options, and finally, 4) Defining procedural success.

We then propose a trial design based on the stage of the disease with suggested criteria for patients' selection.

Challenges and considerations in patients' selection for TTVI

Assessment of TR

Accurate knowledge of the TV anatomy, determination of the TR mechanism, and precise grading of the TR severity and associated right ventricular (RV) dysfunction are among the first challenges faced when considering TTVI.

A- TV anatomy: The TV apparatus is a complex and heterogeneous structure[8] comprised of the leaflets, annulus, chordae, papillary muscles, and right atrial (RA) and ventricular myocardium (Fig. 1). While conventionally thought to have three leaflets (anterior, septal, and posterior), numerous reports have found the number of leaflets to be variable, commonly bicuspid or quadricuspid.[9–11] Compared to the mitral valve apparatus, the tricuspid annulus is larger and rarely calcified, the leaflets are thinner, and the number and shape of the supporting papillary muscles and chordal attachments vary. Also, the TV and pulmonic valves are separated, and not in continuity as is the case for the left-sided valves.[12]

B- Etiology of TR: Primary TR, whether congenital or acquired (rheumatic, carcinoid, iatrogenic, endocarditis, lead-related) is uncommon. In about 90% of the cases, TR is functional or secondary with two frequently coexistent mechanisms: right annular dilation secondary to pulmonary hypertension (whether related to left-sided disease or lung disease) with subsequent RV dilation/dysfunction and associated leaflet tethering, and/or RA dilation from concomitant atrial fibrillation (AF) with associated annular dilation.[13]

C- Grading TR severity: Echocardiography remains the mainstay modality for TR assessment and quantification. However, judging the severity of TR by echocardiography is challenging due to several reasons, including inter-reader variability, dependence on image quality and scanning efforts, and heavy reliance on color flow Doppler.[14] Current guidelines[15] advocate for the integration of quantitative measures (Fig. 2) and adopt the following cutoffs to define severe TR: A vena contracta ≥0.7 cm, an effective regurgitant orifice area (EROA) of ≥0.40 cm^2, and a regurgitant volume ≥ 45 mL. However, there are two main limitations of the current approach:

a- As stated in the guidelines document, the clinical experience in the quantitation of TR is limited, and most echocardiographers still rely solely on a visual qualitative assessment, which commonly underestimates TR severity.

b- Current staging scheme into mild, moderate, and severe TR seems insufficient in capturing the entire spectrum of severe TR observed in patients currently enrolled in the TTVI trials.[16] As a result, some have proposed expanding the "severe" grade to include very severe (or massive) and torrential TR.[17]

Cardiac magnetic resonance (CMR) may be a more accurate alternative for TR quantification by allowing measurement of regurgitant volume and/or fraction,[18,19] however, frequently, these patients are in AF, making it difficult to account for beat-to-beath variability. In addition, follow-up CMR assessment after TTVI may be affected by device-related artifact.

D- Assessment of RV volume and function: Similarly to TR grading, RV size and function determination by standard 2D transthoracic

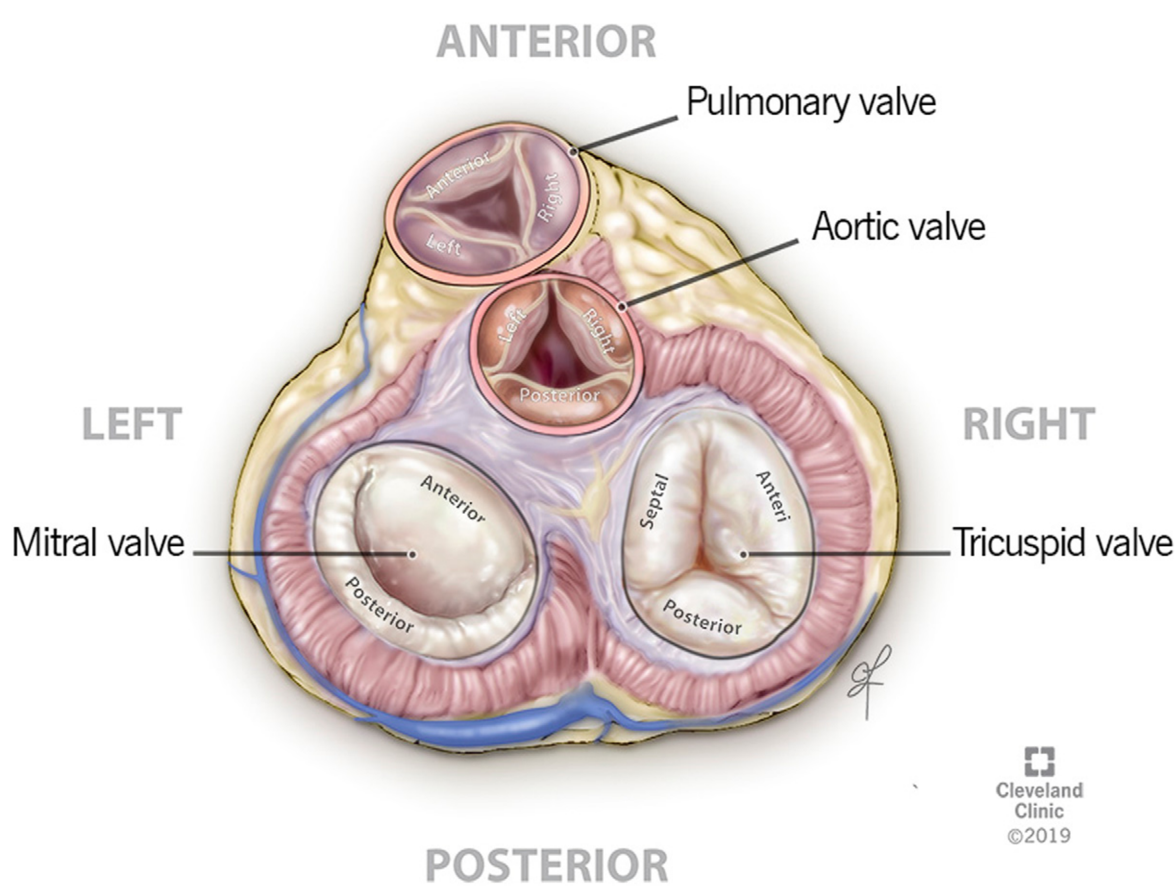

Fig. 1. Anatomy of the tricuspid valve.

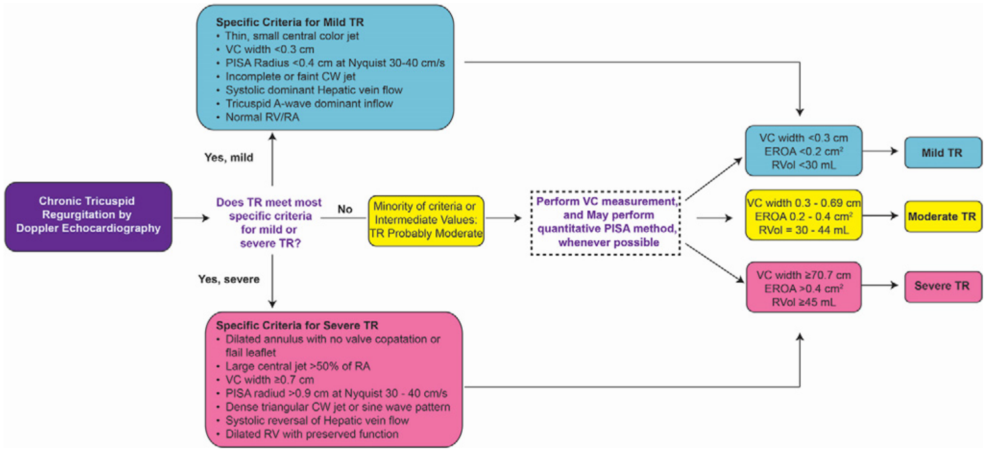

Fig. 2. Integrative approach for TR assessment. Adapted from the guidelines.[15] TR = tricuspid regurgitation, VC = Vena Contracta; RV = right ventricle; RA = right atrium; PISA: proximal isovelocity surface area; EROA: effective regurgitant orifice area; RVol = regurgitant volume.

echocardiography is suboptimal given RV complex structure, the overwhelmingly qualitative current assessment, and the mostly linear two-dimensional measures frequently used (basal annular dimension, tricuspid annular plane systolic excursion) despite the guidelines advocating for more three dimensional assessment.[20] Newer measures may be more reliable such as RV strain, dP/dT, and RV-Pulmonary Artery coupling, but these are not yet well-validated or widely adopted. CMR is the gold standard in RV assessment but again suffers the same limitations as described above. Multiphasic gated cardiac computed tomography has emerged as an important alternative imaging modality but requires an appropriate modern scanner and imaging protocol, and administration of intravenous contrast (which can worsen renal function and chronic kidney disease, commonly seen in these patients). Table 1 lists some of the main quantitative parameters for RV size and function assessment via various imaging modalities.[20–23] Furthermore, it is unclear what defines RV systolic functional impairment in the presence of significant TR.

Understanding the natural history of the disease

A- Will TR improve solely with left-sided therapy? Historically, there has been a misconception that functional TR will improve after correction of the primary left-sided disease, and therefore does not need specific intervention.[24] However, it has been shown that TR continues to progress in a significant number of patients despite successful treatment of left-sided disease,[25,26] with worsening and sometimes the irreversible onset of RV dilation and dysfunction. This has led to an increasingly recognized need to specifically address TR.[27]

B- Is the severity of TR the only matrix? It is important to recognize that functional TR is not a primary valvular problem per se. It is the result of a disease process that leads to right atrial, RV enlargement/dysfunction with associated tricuspid annular dilation and TV leaflets tethering resulting in lack of coaptation with the onset of TR. A proposed staging scheme of functional TR describes three stages based on TR severity, annular dimension, and leaflet coaptation.[28] Since the disease process starts with annular dilation, concomitant tricuspid annuloplasty at time of mitral valve surgery has been advocated for tricuspid annular dilation irrespective of the degree of regurgitation.[29]

Another staging scheme more tailored towards TTVI[6] also has three stages based on annular dilation, TR severity, and clinical right-sided heart failure: Stage 1: annular dilatation without TR, Stage 2: progression to TR without right heart failure(HF), and finally stage 3 with severe TR and onset of right HF.

Knowledge of currently available therapeutic options

There are three broad categories of management options for TR: medical therapy, surgical repair or replacement, and the emergent TTVI.

A- Medical therapy: Optimal medical therapy is not well established. Important elements of medical therapy are primarily loop-diuretics along with aldosterone antagonists when permitted by renal function. Beyond this, there are not many important classes

Table 1
Multimodality assessment of right ventricular volume and function.

Assessment	Parameter	Abnormality threshold
Echocardiography[20]		
Size	Basal diameter (mm)	>41 mm
	EDV indexed to BSA (mL/m^2)	>87 for men; >74 for women
Function	TAPSE (mm)	<17
	Doppler S wave (cm/s)	<9.5 (for pulsed Doppler); <6.0 (for color Doppler)
	Fractional area change (%)	<35
	Free wall 2D Strain	>−20 (< 20 in magnitude with the negative sign)
	3D EF (%)	<45
Cardiac magnetic resonance[21]		
Size	EDV indexed to BSA (mL/m^2)	>128 for men; >110 for women
Function	EF (%)	<40 for men; <45 for women
Cardiac computed tomography[22,23]		
Size	EDV indexed to BSA (mL/m^2)	>120 for men; >102 for women
Function	EF (%)	<51 for men; <54 for women

RV = Right Ventricle; EDV = End-Diastolic Volume; BSA = Body Surface Area; TAPSE = tricuspid annular plane systolic excursion; EF = Ejection Fraction.

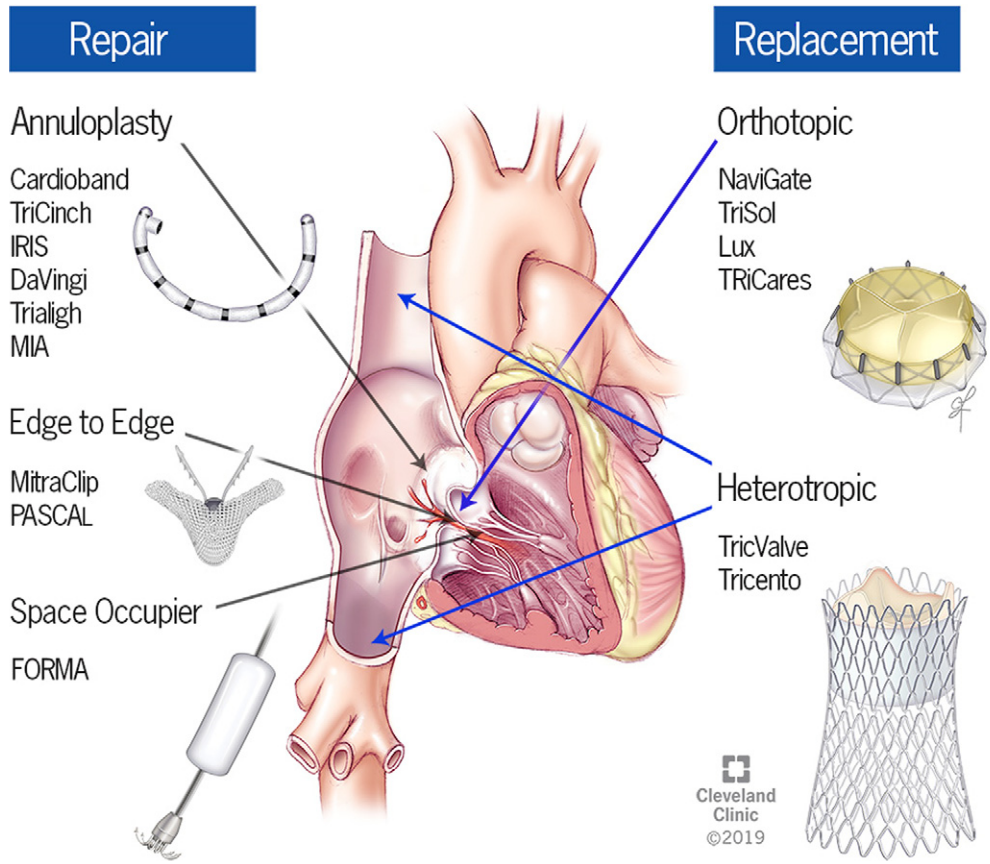

Fig. 3. Current available transcatheter tricuspid valve interventions.

of therapy that are considered the standard of care for treatment of TR. This makes it difficult to use guideline-directed medical therapy as a comparator to device treatments.

B- Surgical therapies and indications:

a- Techniques: Surgical management of functional TR typically consists of tricuspid valve repair with annuloplasty (sutures, rings, and bands). However, in extreme cases with severe tricuspic annular enlargement and RV dysfunction, repair may not be feasible or successful, and TV replacement is pursued.

b- Indications: American and European guidelines[30,31] for the indications TV surgery in secondary TR are similar and largely based on expert opinion (level of evidence C) reflecting the paucity of strong data supporting these recommendations. There is no class I indication for isolated TV intervention. TV surgery is recommended for patients with TR undergoing left-sided surgery if severe, or in the case of mild/moderate TR, if associated with TA dilation (≥40 mm or ≥21 mm/m^2), pulmonary hypertension or right HF. However, outside of left-sided valve surgery, there is no class I or II indication for intervention in secondary TR, even when refractory to standard medical therapy. This results in a large number of patients with secondary TR and various degrees of RV dilation/dysfunction and pulmonary hypertension managed solely with diuretics and deemed for poor outcomes in terms of morbidity and mortality.

C- Emerging TTVI (Fig. 3)

a- Techniques: Multiple TTVI technologies have recently emerged.[32] These can be grouped broadly into repair (TTVr) or replacement (TTVR).

Table 2
Proposed tricuspid valve trial design according to disease stage.

Stages of TV disease	Treatment options for comparison	Outcome	Rationale for the study	Challenges
Stage 1 Annular dilation without TR	Surgical annular reduction	Annular size TR development	Available surgical literature for patients undergoing cardiac surgery	Non-clinical outcomes typically not enough for device approval
Stage 2 TR with no clinical RHF	Surgical treatments	TR reduction RV remodeling	Available surgical literature for patients undergoing cardiac surgery	Non-clinical outcomes typically not enough for device approval
Stage 3 TR with RHF	Medical management in high-risk patients Surgery in acceptable surgical risk patients	Clinical parameters for RHF TR reduction RV remodeling	High clinical event rate Can show potential clinical benefit	Optimal medical therapy not well defined Surgery is not a class 1 indication

TV = Tricuspid valve; TR = Tricuspid regurgitation; RHF = right heart failure; RV = Right volume.

1- TTVr: these can be further divided into the anatomy targeted: annuloplasty devices (ring or suture), edge to edge repair, or space occupier (see Fig. 2)

- Annuloplasty: Cardioband (Edwards Lifesciences, Irvine, CA, USA), TriCinch™ (4Tech Cardio Ltd., Galway, Ireland), IRIS (Millipede Inc., Santa Rosa, CA, USA), DaVingi (Cardiac Implants Ltd., Israel), Trialign™ (Mitralign Inc., Tewksbury, MA, USA), MIA™ (Micro Interventional Devices Inc., Newtown, PA, USA), pledget-assisted suture tricuspid valve annuloplasty (PASTA).
- Edge to Edge repair: MitraClip® (Abbott Vascular, Santa Clara, CA, USA) or PASCAL (Edwards Lifesciences),
- Space occupier. FORMA (Edwards Lifesciences).

2- TTVR: these can be also be further divided into orthotopic or heterotopic

- Orthotopic: NaviGate (NaviGate Cardiac Structures, Inc., Lake Forest, CA, USA), TriSol (Trisol Medical, Haifa, Israel), Lux (Ningbo Jenscare Biotechnology Co., Ltd., Ningbo, China), TRiCares (TRiCares SAS, Paris, France).
- Heterotopic: TricValve® (P&F Products & Features GmbH, Vienna, Austria), Tricento® (NVT GmbH, Hechingen, Germany, and NVT AG, Muri, Switzerland).

b- Patients included: It is important to keep in mind that most of the data available on these devices come from early feasibility studies or reports, including high risk and compassionate cases with no control group. Based on a recent report from the largest TTVI registry,[7] which includes multiple devices in various US and European centers, patients currently enrolled are high risk (mean EuroSCORE II of 9) with very severe/torrential TR (mean EROA 0.8 cm2, vena contracta width >1 cm, regurgitant volume 54 mL/beat), and advanced symptoms (95% had NYHA III-IV symptoms with 69% having prior right HF admission), but with no significant RV dysfunction (as evident by their average TAPSE of 16 mm and S-TDI 10 cm/s) or pulmonary hypertension (pre-procedural

SPAP was 41 mmHg). A very promising finding was that TR reduction was associated with improved survival. However, based on the available data, there are still many unknowns regarding optimal patient selection for TTVI in terms of who would benefit, the appropriate timing for the intervention, and which device should be chosen.

Defining procedural success

Unlike left-sided valvular disease, there is no consensus or standardized definitions for the procedural success of TTVI, with lack of consistency in the efficacy and safety endpoints adopted in the multiple reports examining various devices. This highlights the need for an academic research consortium specific to the TV, similar to what has been for aortic and mitral valve interventions,[33,34] that would standardize definitions and endpoints, allowing comparisons between various TTVI reports.

Similarly, most clinical or imaging tools for assessing HF and RV dysfunction and their response to therapy are primarily designed for left-sided disease. These will either need to be customized for right-sided HF/RV dysfunction, or new specific standardized right-sided evaluation means will need to be developed.

Proposed imaging endpoints include TR grade and RV remodeling and function, assessment of which remains problematic, as discussed above. Clinical endpoints would include, in addition to the hard endpoints of death and hospitalization, quality of life measures (customized for right-sided HF), diuretic down-titration, reduction in ascites and edema scales, enhanced functional capacity, and improvement in liver or kidney function.

Proposed TV trial design and considerations in the selection process

Proposed TV trial design

Table 2 presents trial designs based on the stage of disease specifying the comparator treatment option, the proposed outcomes, the rationale for the study, and the anticipated challenges.

When considering patients in stages 1 and 2 (i.e., before the development of right-sided HF) and based on the literature supporting concomitant TV treatment during left-sided cardiac surgery, TTVI would be compared to surgical TV intervention. The main anticipated challenge is the lack of clinical outcomes, as these patients do not exhibit symptoms specific to their right-sided valvular disease, which is typically required for device approval. Also, solely relying on imaging endpoints suffers the current significant limitations in the quantitative assessment of TR, annular dilation, and RV size and function.

Patients with clinical right-sided HF due to severe TR (stage 3) seem the most suited for initial TTVI trials. Their current options include TV surgery if deemed surgical candidates, or medical therapy in high-risk cases. Both of these options carry significant morbidity and mortality, with high anticipated clinical events rate, giving TTVI potential to show clinical benefits if efficacious. The challenges in this scenario are multiple and include the lack of class I guideline supported surgical indication for these patients, the ill-defined optimal medical therapy, and the absence of consistency or standardization in the definition of clinical and imaging outcomes. Also, this group of patients is vastly heterogeneous, and several considerations come into play when selecting specific patients for enrollment.

Considerations in the selection process

An important initial consideration is to exclude patients where treatment of TR is unlikely to change outcomes. One such group consists of patients with severe TR and advanced, likely irreversible RV dysfunction (appropriate cutoffs would need to be defined). As outlined, it may be important to further classify severe TR as very severe or torrential. This distinction is important to properly characterize patients for inclusion, as well as to determine the success of treatment when residual TR may still be moderate or severe in degree but significantly less compared to before TTVI.

Other exclusion criteria would include severe pulmonary hypertension, or concomitant left-sided disease and significant comorbidities (frailty, cirrhosis, dialysis, advanced lung disease for example) that would preclude clinical benefit despite a reduction in TR. Anatomic criteria for exclusion and the presence of transvalvular leads would be device-specific.

Another important consideration is the potential for concomitant TTVI during percutaneous mitral therapy. If the latter gets approved for functional mitral regurgitation, a trial for TTVI in conjunction with mitral therapy can be considered. Clinical endpoints may be difficult to prove as these patients may not have significant right HF (stage 2). However, halting the progression of TR, as well as the prevention of RV dilatation or dysfunction, can be potentially demonstrated in this population. Treatment of TR in patients undergoing percutaneous mitral regurgitation therapy may, therefore, become one of the more important indications for TTVI.

Conclusion

Patients requiring isolated TV intervention for severe TR pose significant challenges: they constitute a widely heterogeneous group for whom optimal medical therapy is not well defined. Isolated TV surgery remains rarely indicated, and when performed of higher risk. Accurate assessment of right-sided valvular and RV function is suboptimal, and the best timing for intervention remains unknown. Multiple TTVI technologies are emerging, but are still in their early stages. The identification of the subset of patients who will benefit remains uncertain. It is also unclear whether some patients might benefit from combination therapy (i.e., edge to edge repair + annuloplasty). Necessary first steps would be to standardize definitions and specific outcomes in this patient population and to advocate for more precise and quantitative valvular and RV assessment. This will require multimodality imaging integration for more precise quantification. With ongoing research and device development, our understanding of this complex disease entity and management options will improve.

Disclosures

None.

Declaration of competing interest

None.

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