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Surgical approach to combined mitral and tricuspid valve disease: good neighbourhood rules

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Tricuspid regurgitation afflicts more than one-third of patients with mitral valve disease during their clinical history, and negatively affects their outcomes, increasing mortality and hospitalizations for heart failure and reducing the quality of life. A renewed interest in the 'neglected valve' has increased the frequency of the combined treatment of these two diseases. Undoubtedly necessary in patients with degenerative mitral valve disease in the presence of two severe valve defects, tricuspid annuloplasty has proven to be safe and effective even if performed prophylactically, when tricuspid annular dilation coexists with primary mitral dysfunction. In the absence of survival benefits, however, this additional surgical procedure increases the risk of high-grade atrio-ventricular blocks and the need for a definitive pacemaker. On the other hand, the role of surgery has been scaled down in patients with functional mitral and tricuspid regurgitation. In this context, a multidisciplinary approach is needed and transcatheter alternatives are increasingly the chosen treatment option. A new therapeutic algorithm is therefore looming on the horizon. In the future, the treatment of tricuspid and mitral valve disease may be considered two potentially distinct and successive phases of an integrated heart failure patients care process.

Introduction

In patients referred for mitral valve surgery, haemodynamically significant tricuspid regurgitation (TR) often coexists. In most cases, the tricuspid valve defect is secondary to right ventricular dilatation (due to pressure/volume overload in the context of left heart pathology) or tricuspid annular dilatation (in the context of long-lasting atrial fibrillation). More rarely, degenerative or rheumatic pathology involving the mitral valve also affects the tricuspid leaflets, leading to the coexistence of a primary bi-valvular defect.

As a matter of fact, more than 30% of patients with degenerative mitral regurgitation (MR) have an at least moderate TR at the time of mitral surgery, and up to a third of patients with significant mitral stenosis have TR.[1]

The prevalence of TR is also particularly high in patients with secondary ischaemic MR. In fact, significant TR is found in more than 30% of patients undergoing coronary artery bypass grafting (CABG) and mitral surgery.[1]

The coexistence of a bi-valvular defect has a significant prognostic impact. A recent prospective community study conducted on subjects over 65 years old (OxVALVE registry)[2] has indeed shown a 5-year survival rate of 59.4% in patients with an at least moderate MR and TR, 20% less if compared to subjects with isolated mitral or tricuspid valve regurgitation. Moreover, the latter are four times less likely to experience cardiac death.[2] A careful evaluation of any coexisting tricuspid defect is therefore imperative in patients referred for mitral surgery.

For years, however, TR has been considered a 'tolerable' anomaly, underdiagnosed and rarely surgically treated. This conservative approach was justified by the belief that, in patients with left heart valvular

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diseases, secondary TR would disappear once the mitral or aortic pathology was corrected.[1]

Nevertheless, severe TR is an independent predictor of long-term mortality,[2] and several studies have documented shorter survival and worse quality of life in patients undergoing mitral surgery who developed severe TR during follow-up.[1] For this reason, the Cardiology Community has recently shown a renewed interest in the treatment of tricuspid disease in patients with mitral valve pathology.

The aim of this report is to analyse treatment indications and clinical results of mitral and tricuspid bivalvular surgery, distinguishing two different clinical scenarios (*Figure 1*): secondary tricuspid regurgitation in patients with primary mitral valvulopathy and coexistent functional MR and TR, both in the context of ventricular (dilated cardiomyopathy and heart failure) or atrial (atrial fibrillation) pathology.

Tricuspid regurgitation in patients with primary mitral pathology

In patients with both haemodynamically significant mitral regurgitation and stenosis, the pressure/volume overload in the left atrium results in an increase in right ventricular afterload. This condition gradually alters the tricuspid valve apparatus and the right ventricular geometry, leading to the development of TR. Since this is a progressive disease, the absence of TR at the time of left heart surgery does not guarantee the stopping of the pathophysiological process of right ventricular remodelling. Indeed, up to 40% of patients undergoing mitral valve surgery develops significant TR late after surgery,[1] and the pre-existence of annular dilation, indicating a more advanced state of the disease, has been identified as a predictor of TR progression.[1]

For these reasons, correction of tricuspid regurgitation during left heart surgery is indicated if TR is severe (class of recommendation IC) but, even in the absence of significant TR, it should be considered (class of recommendation IIa) in case of annular dilation (septal-lateral diameter ≥ 40 mm or > 21 mm/m^2).[3] This condition is in fact associated with a greater probability of worsening of TR during follow-up. Furthermore, redo surgery for correction of tricuspid valve disease, particularly if carried out late and when signs of right ventricular dysfunction have already developed, is associated with a non-negligible short-term mortality.[1]

An aggressive attitude in TR treatment in this context is corroborated by the results of a series of clinical studies.

Pioneering was, first of all, the work of Dreyfus et al,[4] who prospectively analysed 311 patients undergoing mitral valve surgery. All subjects with tricuspid annular dilation (148 patients, 47.6%), regardless of TR severity,

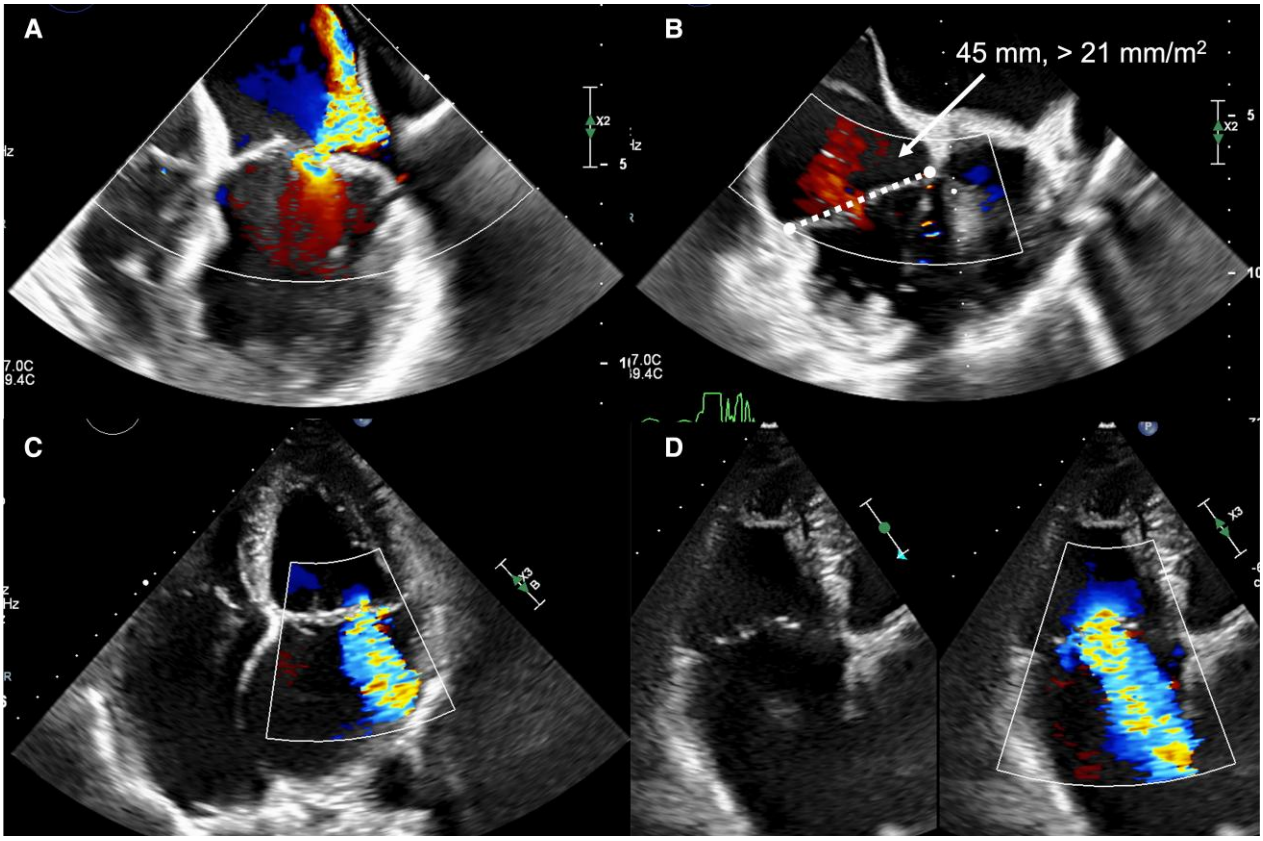

Figure 1 Echocardiographic images of combined mitral and tricuspid valve disease. Severe degenerative mitral regurgitation (*A*) and coexisting non-significant functional tricuspid regurgitation (*B*), but with annular dilation (septal-lateral diameter 45 mm, > 21 mm/m^2) as shown by transesophageal echocardiography. Atrial functional mitral (*C*) and tricuspid (*D*) regurgitation as shown by transthoracic echocardiography.

Table 1 Clinical results of combined mitral and tricuspid valve surgery in patients with primary MR

Type of study	Dreyfus 2005[4] Retrospective	Tam 2019[5] Meta-analysis	Gammie 2022[6] Prospective	Bernal 2010[7] Retrospective	Rankin 2013[8] Retrospective	Crestanello 2004[9] Retrospective
Number of patients undergoing combined mitral and tricuspid surgery	148	11 787	198	153	21 056	2 out of 22 patients with post-actinic valve disease
Pre-operative ejection fraction% (mean ± SD)	61.4 ± 8.7	53.9	64.1 ± 7.1	55.8 ± 11.3	50	52 ± 15
Pre-operative right ventricular function	–	–	Normal in 91.3% of patients	–	–	–
Pre-operative sPAP mmHg (mean ± SD)	39.9 ± 6.7	44.3	–	48.4 ± 15.8	–	–
Etiology of mitral pathology					MS in 24% of cases	
• Degenerative (number of patients)	97	6548	198	0	–	0
• Rheumatic (number of patients)	26	153	0	153	–	0
• Post-actinic (number of patients)	0	0	0	0	–	2
Pre-operative tricuspid regurgitation		Mean 1.67		Isolated TR in 53.6% of the cases, TR + TS in 46.4%	–	–
• No TR (number of patients)	38	–	53	–	–	–
• Mild (number of patients)	92	–	65	–	–	–
• Moderate (number of patients)	18	–	73	–	–	–
• Severe (number of patients)	0	–	1	–	–	–
Tricuspid annulus diameter mm	≥ 70	Mean 36.6	Mean ± SD 42 ± 4.6	–	–	–
Indication to TVr	Any degree of regurgitation if annular dilation	Variable (annular dilation, TR ≥ 2, TR ≤ 2, TR of any degree)	TR ≥ 2 or TR < 2 but annular dilation	Bi-valvular rheumatic involvement	–	Annular dilation
Follow-up duration (mean ± SD)	4.8 ± 2.9 years	6.0 ± 0.64 years	2 years	15.8 years	30 days	3.7 ± 3.3 years
MR at follow-up	Mean ± SD 0.6 ± 0.66	–		–	–	
• No or mild (number of patients)	–	–	162	–	–	1
• Moderate (number of patients)	–	–	16	–	–	0
• Severe (number of patients)	0	–	1	–	–	1
TR at follow-up		72% lower risk of TR ≥ 2 than isolated mitral surgery		–	–	
• No TR (number of patients)	102	–	158	–	–	0
• Mild (number of patients)	41	–	20	–	–	1
• Moderate (number of patients)	5	–	4	–	–	0
• Severe (number of patients)	0	–	2	–	–	1
Need for re-intervention at follow-up	three patients (two MVR and one TVR)	No differences from isolated mitral surgery	–	59 mitral re-operations, 38 tricuspid re-operations; freedom from re-intervention 48.5 ± 5.1% at 20 years	–	one patient
Hospitalizations during follow-up	–	–	nine patients (4.5%)	–	–	–
	eight patients (5.4%)	2.73 times greater risk	28 patients (14.1%), six	–	–	one patient

Continued

Table 1 Continued

Type of study	Dreyfus 2005[4] Retrospective	Tam 2019[5] Meta-analysis	Gammie 2022[6] Prospective	Bernal 2010[7] Retrospective	Rankin 2013[8] Retrospective	Crestanello 2004[9] Retrospective
Need for permanent pacemaker implantation		than isolated mitral surgery	times higher risk than isolated mitral surgery			
Survival	90.3% at 8 years	No differences if compared with isolated mitral surgery	96.8% at 2 years	69.0 ± 3.7% at 10 years	At 30 days MVR + TVR: 83.2%, MVr + TVR: 89.8%, MVR + TVr: 89.7%, MVr + TVr 92%	66% at 5 years

MR, mitral regurgitation; MS, mitral stenosis; MVr, mitral valve repair; MVR, mitral valve replacement; SD, standard deviation; sPAP, systolic pulmonary arterial pressure; TR, tricuspid regurgitation; TS, tricuspid stenosis; TVr, tricuspid valve repair; TVR, tricuspid valve replacement.
The severity of MR and TR was stratified as follows: 0, no regurgitation; 1, mild regurgitation; 2, moderate regurgitation; 3, moderate to severe regurgitation; 4, severe regurgitation.

underwent a simultaneous tricuspid annuloplasty. Patients undergoing bi-valvular surgery, even if TR was less than moderate in most subjects of both groups, had slightly longer in-hospital and long-term survival than those undergoing mitral valve repair alone (at 10 years 90.3% vs. 85.5%, although the difference was not statistically significant). 'Prophylactic' tricuspid annuloplasty in patients with tricuspid annular dilation also proved to improve symptoms more than isolated mitral repair, and showed, for the first time, to have a protective role against the progression of TR after left heart surgery. In fact, at follow-up (4.8 ± 2.9 years on average), TR increased by more than two degrees of severity in 48% of patients undergoing isolated mitral valve repair, but only in 2% of those who also received tricuspid annuloplasty.

Several studies, including two randomized trials, analysed the issue in subsequent years. A summary of the main evidence available is provided by a recent meta-analysis,[5] which compares a total of 11 533 patients who underwent mitral valve surgery and contemporary tricuspid annuloplasty with 55 477 subjects in which only mitral valve intervention was performed. This study did not identify any differences in short-term and long-term mortality between the two groups. Regardless of pre-operative tricuspid regurgitation severity, tricuspid annuloplasty has nevertheless proved to be able to reduce late onset of significant TR, while increasing more than twice the risk of definitive pacemaker implantation.

These results were also confirmed by another randomized study,[6] not included in the previous analysis and with a larger sample size, which enrolled 401 patients with significant degenerative MR and randomly divided them into two groups: isolated mitral surgery and mitral surgery with concomitant tricuspid annuloplasty. This study confirmed the protective role of 'prophylactic' tricuspid repair in preventing the development of significant TR, albeit without a clear benefit in terms of mortality and with a significant rate of definitive pacemaker implantation (14% of subjects undergoing tricuspid annuloplasty).

Mitral and tricuspid pathology in patients with rheumatic disease and post-actinic valve dysfunction

In the context of rheumatic disease, the inflammatory rearrangement of leaflets and subvalvular apparatus can affect both mitral and tricuspid valve, usually leading to the coexistence of stenosis and regurgitation. The prevalent valvular defect and the severity of rheumatic involvement are two of the main determinants of surgical reparability in this context. While in patients with functional TR and rheumatic mitral valve pathology, in fact, it is true what stated so far,[5] bi-valvular repair in case of rheumatic involvement of both mitral and tricuspid valve has shown unsatisfactory results, with a 15-year survival of 57% and a 20-year reoperation rate of 48%.[7] In this context, therefore, valve replacement is often required, although associated with a higher

Table 2 The clinical results of the surgical and interventional treatment of combined functional mitral and tricuspid regurgitation

Type of study	Calafiore 2009[5] Retrospective	Koppers 2013[5] Retrospective	Mehr 2020[15] Retrospective	Takahashi 2020[16] Retrospective
Number of patients undergoing combined mitral and tricuspid intervention	51	55	122	45
Type of treatment	Surgery: 39 MVr, 12 MVR	Surgery	Transcatheter (Mitraclip)	Surgery (combined mitral and tricuspid annuloplasty)
Pre-operative ejection fraction % (mean ± SD)	28.5 ± 0.054	–	22 patients < 30%, 44 patients 30–50%	63 ± 8.9
Pre-operative right ventricular function	Mean TAPSE ± SD 14.1 ± 2.5 mm	Mean RVFAC ± SD 30 ± 10%	Mean TAPSE ± SD 15.7 ± 4 mm	–
Pre-operative sPAP mmHg (mean ± SD)	41.2 ± 11.5	44 ± 19	72 patients with sPAP > 40 mmHg	37 ± 9
Pre-operative tricuspid regurgitation		Mean ± SD 1.8 ± 1.0		Mean ± SD 2.0 ± 0.7
• No TR (number of patients)	0	–	0	0
• Mild (number of patients)	0	–	0	15
• Moderate (number of patients)	11	–	0	17
• Moderate to severe (number of patients)	24	–	0	1
• Severe (number of patients)	16	–	69	13
• Massive (number of patients)	–	–	53	0
Tricuspid annulus diameter mm (mean ± SD)	–	37 ± 6	47 ± 8	–
Indication to tricuspid valve repair	Surgeon's choice in patients with TR ≥ 2	TR> 2 or annular dilation (tricuspid annulus diameter > 40 mm)	Patients with indications for TR treatment according to guidelines but at high surgical risk	All patients, regardless of TR severity
Follow-up duration	Median 66 months	Mean 15 months	Approximately 1 year for every patient	Median 932 days
Mitral regurgitation at follow-up		–		Mean ± SD 0.9 ± 0.5
• No MR (number of patients)	–	–	3	19
• Mild (number of patients)	–	–	85	19
• Moderate (number of patients)	–	–	26	3
• Severe (number of patients)	1	–	2	1
Tricuspid regurgitation at follow-up	Mean ± SD 0.7 ± 0.7	Mean ± SD 0.6 ± 0.7		Mean ± SD 0.8 ± 0.5
• No TR (number of patients)	–	–	1	25
• Mild (number of patients)	33	–	48	16
• Moderate (number of patients)	6	–	48	0
• Moderate to severe (number of patients)	1	–	–	0
• Severe (number of patients)	1	–	19	1
• Massive (number of patients)	–	–	6	0
Need for re-intervention at follow-up	–		–	three patients

Continued

Table 2 Continued

Type of study	Calafiore 2009[5] Retrospective	Koppers 2013[5] Retrospective	Mehr 2020[15] Retrospective	Takahashi 2020[16] Retrospective
Hospitalizations during follow-up	—	Freedom from hospitalizations at 15 months: 60%	—	three patients
Need for permanent pacemaker implantation	—	—	—	—
Survival	74.5 ± 5.1% at 5 years	82% at 15 months	83.6% at one year	95% at 5 years

MR, mitral regurgitation; MVr, mitral valve repair; MVR, mitral valve replacement; RVFAC, right ventricular fractional area change; SD, standard deviation; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation. The severity of MR and TR was stratified as follows: 0, no regurgitation; 1, mild regurgitation; 2, moderate regurgitation; 3, moderate to severe regurgitation; 4, severe regurgitation

mortality if compared with bi-valvular repair.[8] The latter has yielded disappointing results also in patients with post-actinic valve regurgitation. Fibrosis and calcification of the leaflets induced by radiation therapy are in fact associated with early relapse of significant regurgitation (up to 32% at 5 years after surgery),[9] in a population made of complex patients, often with ventricular dysfunction, multivalvular involvement or coronary artery disease.[9]

Clinical results of combined mitral and tricuspid valve surgery in patients with primary MR are summarized in *Table 1*.

Coexistent functional mitral and tricuspid regurgitation

In patients with coexistent functional MR and TR, the leaflets are structurally normal and valve incompetency is one of the characteristics of a complex picture, determined by progressive ventricular or atrial dilation and dysfunction.

The subtype associated with biventricular impairment is typical of patients with chronic heart failure in the context of cardiomyopathies of various etiology (in most cases ischaemic). In these subjects, the symptoms and outcomes are closely correlated with the extent of ventricular dysfunction and the natural history of underlying cardiomyopathy. For these reasons, the optimization of medical treatment and the implantation of a cardiac resynchronization therapy (CRT), whenever indicated, represent the first therapeutic approach, capable of inducing reverse ventricular remodeling and reducing mortality.[3] In this context, the right timing of corrective interventions on valve defects is still object of debate and, according to the latest guidelines,[3] any therapeutic choice should be made after a multidisciplinary discussion by the Heart Team. Although secondary to ventricular pathology, in fact, both MR and TR are associated with a worsening of symptoms and an increase in mortality in patients with heart failure, particularly if the regurgitation is severe.[3,10] As a consequence, delaying corrective interventions could further worsen biventricular systolic function.

Significant TR characterizes more than 30% of patients undergoing mitral surgery for isolated secondary MR.[1] Tricuspid annuloplasty in this setting has shown to reduce the severity of TR at follow-up, with no clear survival benefits. Some studies, on the contrary, have indicated a higher mortality and a higher hospitalization rate in patients undergoing simultaneous tricuspid surgery, probably because of the greater complexity of subjects with functional MR who also develop significant TR.[5,11]

In any case, the role of surgery in secondary MR has been greatly scaled down over the years. Both isolated mitral valve repair and replacement in this subgroup of patients are in fact associated with a high periprocedural risk and a high rate of recurrence of significant regurgitation in case of valve repair (up to 32% at 12 months) in the absence of proven survival benefits.[12] For these reasons, in the context of severe functional MR, mitral valve surgery remains indicated (class of recommendation IB) in patients undergoing CABG or surgical

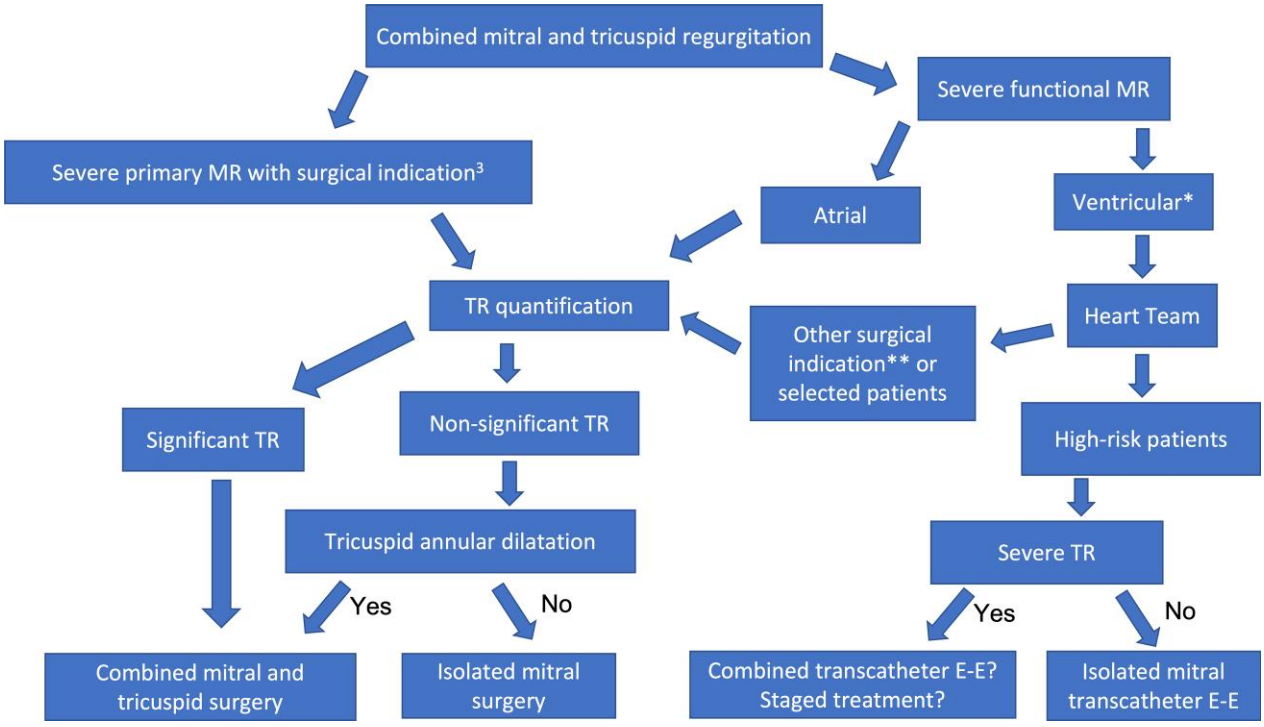

Figure 2 Therapeutic algorithm in patients with combined mitral and tricuspid regurgitation. E-E, edge-to-edge; MR, mitral regurgitation; TR, tricuspid regurgitation; *, in symptomatic patient despite optimal medical therapy; **, coronary artery bypass grafting or surgical correction of other valvulopathies.

correction of other valvulopathies.[3] In the case of isolated mitral pathology, although the surgical option is contemplated in selected cases, judged operable by the Heart Team, transcatheter therapeutic options are increasingly being used.

Among the variety of devices undergoing clinical and preclinical validation, the treatment of functional MR with percutaneous edge-to-edge (MitraClip system) represents the only alternative to have found its own legitimacy. In fact, two randomized trials (COAPT[13] and MITRA-FR[14]) demonstrated the efficacy and safety of this device in subjects with severe functional MR, still symptomatic despite optimal medical therapy. In COAPT patients, 16.4% had an at least moderate TR.[13] The coexistence of significant tricuspid valve disease in this subgroup has been linked to an increase in mortality and hospitalizations for heart failure, thus a growing interest has developed about the possibility of correcting both valve defects percutaneously. The analysis of data collected in two multicentric Registries (TriValve and TRAMI) demonstrated the feasibility and efficacy of the combined transcatheter mitral and tricuspid edge-to-edge (TMTEE) in a population of 122 patients. However, the procedure proved to be more effective in resolving left than right valvular defect. After TMTEE, in fact, 75.9% of the subjects had mild or trivial MR but only 40% showed a less than moderate TR. Furthermore, 20% of the patients were still affected by severe or massive TR. However, concomitant treatment of MR and TR was associated with a two-fold lower one-year mortality rate if compared with mitral-only percutaneous edge-to-edge repair.[15]

It is also true that a reduction in TR degree is anyway recorded in a variable proportion of patients (up to 33%)[15] undergoing isolated percutaneous mitral valve repair. For this reason, in absence of the increased periprocedural risks associated with redo surgery, the transcatheter alternatives pave the way for a gradual approach to combined mitral and tricuspid dysfunction, with a deferral of non-severe TR treatment, even in case of annular dilation. This will later be performed only in patients in whom tricuspid valve disease progresses.

Atrial functional MR and TR deserve a separate discussion. These entities are found in patients with long-lasting atrial fibrillation, in whom the inability of normally structured valve leaflets to coaptate is due to a progressive annular dilation of both atrio-ventricular valves, in the absence of left ventricular dysfunction. Although combined percutaneous approaches have been described also in this context, especially in patients with high surgical risk, the annuloplasty of both valves (with potential mitral leaflets manipulation in case of an excessive coaptation gap) has proven to reduce significantly both MR and TR (98% of patients with less than moderate MR and TR at a mean follow-up of 2 years),[16] with a marked improvement in functional class as well.

The clinical results of the surgical and interventional treatment of combined functional mitral and tricuspid regurgitation are summarized in *Table 2*.

Conclusions

In the context of a recent renewed interest in tricuspid disease, more and more patients with mitral valve disease require simultaneous surgery on the tricuspid valve.

In patients with degenerative MR, combined tricuspid annuloplasty is safe, and is able, if performed prophylactically, to reduce the late incidence of significant TR, with an increase however in the risk of definitive pacemaker implantation.

On the other hand, the role of surgery has been scaled down in the treatment of secondary mitral and tricuspid valve disease. In fact, if for atrial functional forms surgical valve repair represents an excellent solution for the simultaneous treatment of bi-valvular regurgitation, the secondary ventricular subtype requires an integrated approach. In this context, the increasing diffusion of transcatheter therapies opens the way to a new therapeutic algorithm (*Figure* 2), based on a staged treatment of the two valvular diseases and thus reserving tricuspid intervention only for patients who develop significant TR during their clinical course.

Conflict of interest: None declared.

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