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Transcatheter tricuspid interventions are performed too late: pros and cons

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Introduction

The rapid evolution of cardiovascular procedures has brought transcatheter tricuspid valve interventions (TTVI) to the forefront of contemporary practice. Early diagnosis of tricuspid regurgitation is difficult because of the subclinical course of the early phases, and patients are often referred to heart valve centres in the advanced stages.

Timely TTVI might improve patient outcomes, prevent further right ventricular deterioration, and reduce the burden on healthcare systems, with such benefits being questionable in end-stage patients. On the other hand, the risks and potential complications associated with TTVI, coupled with the lack of long-term data, may warrant a more conservative approach. Whether early TTVI should be offered to patients with tricuspid regurgitation is still matter of a complex debate.

Pros

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It is known that patients with severe tricuspid regurgitation (TR) often present at a late stage when the signs and symptoms of right-sided heart failure (HF) are very advanced. Indeed, the clinical course of TR, especially when isolated, is slow and progressive, with early stages being subclinical and characterised by unspecific and often underestimated symptoms (i.e., fatigue, dyspepsia). Surgery of isolated TR in patients with a late indication is burdened by high in-hospital mortality, and medical therapies (i.e., diuretics) are often ineffective at these late stages. TTVI is emerging as a possible treatment option, but its effectiveness and optimal timing are still a matter of debate[1]. In the multinational, retrospective TriValve Registry, which included patients undergoing TTVI, procedural success was associated with a higher survival rate, as compared to procedural failure. A coaptation gap >6.5 mm and an effective regurgitant orifice area >0.695 cm^2 were found to be independent predictors of procedural failure after edge-to-edge repair[2]. Accordingly, compared with severe TR, massive or torrential TR at baseline was associated with a higher rate of clinical events after TTVI[3]. Notably, the majority of the procedures were performed with old-generation edge-to-edge devices.

Severe right ventricular dysfunction was reported to be associated with poor outcomes despite successful TTVI. Interestingly, a propensity-matched analysis showed a prognostic advantage of TTVI, as compared to conservative management, only in patients with a moderate reduction in right ventricular function[4]. Of note, many challenges in the evaluation of right ventricular function in patients with severe TR are worth considering.

In addition, hepatic congestion and renal failure were found to be associated with an increased risk of mortality, independently from the procedural success of TTVI, baseline symptoms and right ventricular function[5]. Indeed, long-standing visceral congestion may lead to irreversible organ damage that persists after TR correction.

Finally, a precapillary component of pulmonary hypertension seems to be associated with worse prognosis after TTVI[6]. It can be due to conditions requiring specific treatments (i.e., lung disorders) or represent a mere bystander of end-stage left-sided HF.

All these findings suggest that a late transcatheter treatment of TR does not lead to a benefit in terms of hard endpoints (i.e., mortality and HF hospitalisation). Specifically, it is expected that

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patients with severe TR and severe right ventricular dysfunction, renal and hepatic damage, as well as precapillary pulmonary hypertension experience a poor prognosis despite an effective TTVI. Notably, large leaflet gaps and/or massive or torrential TR, which are often observed in advanced stages, may limit the likelihood of obtaining an effective and durable TR correction by using repair techniques.

Thus, although further research is definitely needed to support this hypothesis, early identification of patients with severe TR may have a major role in improving procedural results and prognosis.

Additionally, improvements in symptoms and quality of life after TTVI need to be explored in the setting of advanced right-sided HF. These endpoints are difficult to assess but have raised interest, since it is known that patients with advanced HF may prefer trading years of life for a better quality of life. The TRILUMINATE Pivotal Trial[7] comparing transcatheter tricuspid edge-to-edge repair versus medical therapy in patients with at least severe TR, showed a significant improvement in quality of life in the device versus control arm. However, this population was at low risk, as they were probably enrolled at an early stage.

In conclusion, TTVI may be futile in preventing death and HF hospitalisation in patients with advanced HF. Prospective studies, exploring both hard endpoints and patient reported outcomes, are urgently needed to support early diagnosis and treatment of severe TR.

Conflict of interest statement

M. Adamo received speaker honoraria from Abbott Structural Heart. C.I. Radulescu has no conflicts of interest to declare.

Cons

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Severe TR is independently associated with mortality, heart failure and poor quality of life. Although medical management of severe TR with diuretics remains the cornerstone of therapy, TTVI, which avoids the high risk associated with isolated tricuspid surgery, has emerged as a promising alternative. The optimal timing of intervention for patients with isolated functional TR is controversial; current guidelines are conservative, with surgery given a class IIa recommendation in the absence of severe right ventricle/left ventricle (RV/LV) dysfunction and pulmonary hypertension, while TTVI receives only a class IIb recommendation for inoperable patients[8]. TR often begets further worsening of TR; however, disease progression usually occurs slowly, over years or decades in the majority of patients. In contrast to mitral regurgitation, TR is often well tolerated, given the high capacitance of the systemic venous circulation. As a result, many patients may remain asymptomatic and do not present for medical attention until the disease has progressed to the later stages, sometimes with severe RV dysfunction and renal/hepatic failure, rendering any intervention futile. As a result, early diagnosis and treatment seems reasonable, but do we have evidence?

The TRILUMINATE Pivotal Trial demonstrated for the first time that transcatheter edge-to-edge repair (TEER) with the TriClip system (Abbott) improved quality of life, with a Kansas City Cardiomyopathy Questionnaire score increase of 12 points compared to medical therapy alone at 1-year follow-up. However, no differences in mortality or heart failure hospitalisation (HFH) were observed. Previous natural history studies of TR patients had indicated a significant symptom burden requiring HFH and an increased risk of mortality; a propensity-matched analysis from the TriValve Registry suggested a reduction in mortality and HFH with TTVI (predominantly TEER) compared with medical therapy[9]. In contrast to these studies, over 40% of patients in TRILUMINATE were in New York Heart Association (NYHA) Class I/II, and only 25% of patients had an HFH in the preceding year, suggesting that trial enrolment and intervention was performed relatively early in their disease course. Furthermore, a subgroup analysis indicated similar benefits of TEER in patients with RV dysfunction (RV end-diastolic diameter >5 cm, tricuspid annular plane systolic excursion <1.7 cm and cardiac output <4 L/min) and chronic kidney disease, suggesting that patients further along in their disease course also derived symptomatic benefit and were not treated too late. Notably, the trial mainly enrolled patients with atrial functional TR and/or HF with preserved ejection fraction; patients with LV dysfunction made up only ~10% of the cohort, so conclusions about this important subset of TR patients cannot be drawn.

Mortality was lower than expected in TRILUMINATE (<10% in both groups at 1 year, with follow-up planned for 5 years) compared with natural history studies, reflecting the less comorbid population enrolled. These reassuring data suggest that close follow-up and optimisation of medical therapy in similar TR patients is a safe and effective strategy, reserving tricuspid intervention for those with persistent symptoms or HFH. However, it remains an open question whether TTVI will reduce mortality or HFH in patients commonly encountered in clinical practice who have more advanced disease (i.e., recurrent HFH, renal/liver failure, moderate/severe LV or RV dysfunction). Multiple randomised trials are currently underway (e.g., TRICI-HF, TRI-FR, CLASP II TR, TRISCEND II) to determine the impact of various TTVI devices at different stages of disease progression; these will greatly refine our patient selection strategy and understanding of the disease. In the meantime, there is currently no strong evidence that transcatheter tricuspid valve interventions are performed too late. Instead, clinicians should be proactive in the early diagnosis and medical management of TR, remaining vigilant for signs of disease progression with early referral to an experienced heart valve centre.

Conflict of interest statement

N.P. Fam is a consultant to Edwards Lifesciences, Abbott, and CardioValve. S.N. Bakar has no conflicts of interest to declare.

References

1. Praz F, Muraru D, Kreidel F, Lurz P, Hahn RT, Delgado V, Senni M, von Bardeleben RS, Nickenig G, Hausleiter J, Mangieri A, Zamorano JL, Prendergast BD, Maisano F. Transcatheter treatment for tricuspid valve disease. *EuroIntervention.* 2021;17:791-808.

2. Mehr M, Taramasso M, Besler C, Ruf T, Connelly KA, Weber M, Yzeiraj E, Schiavi D, Mangieri A, Vaskelyte L, Alessandrini H, Deuschl F, Brugger N, Ahmad H, Biasco L, Orban M, Deseive S, Braun D, Rommel KP, Pozzoli A, Frerker C, Näbauer M, Massberg S, Pedrazzini G, Tang GHL, Windecker S, Schäfer U, Kuck KH, Sievert H, Denti P, Latib A, Schofer J, Nickenig G, Fam N, von Bardeleben S, Lurz P, Maisano F, Hausleiter J. 1-Year Outcomes After Edge-to-Edge Valve Repair for Symptomatic Tricuspid Regurgitation: Results From the TriValve Registry. *JACC Cardiovasc Interv.* 2019;12:1451-61.

3. Miura M, Alessandrini H, Alkhodair A, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter J, Himbert D, Ho E, Juliard JM, Kaple R, Besler C, Kodali S, Kreidel F, Kuck KH, Latib A, Lauten A, Monivas V, Mehr M, Muntané-Carol G, Nazif T, Nickenig G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodés-Cabau J, Schäfer U, Schofer J, Sievert H, Tang GHL, Thiele H, Rommel KP, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Maisano F, Hahn RT, Taramasso M; TriValve Investigators. Impact of Massive or Torrential Tricuspid Regurgitation in Patients Undergoing Transcatheter Tricuspid Valve Intervention. *JACC Cardiovasc Interv.* 2020;13:1999-2009.

4. Schlotter F, Miura M, Kresoja KP, Alushi B, Alessandrini H, Attinger-Toller A, Besler C, Biasco L, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Estevez-Loureiro R, Fam N, Gavazzoni M, Himbert D, Ho EC, Juliard JM, Kalbacher D, Kaple R, Kreidel F, Latib A, Lubos E, Ludwig S, Mehr M, Monivas V, Nazif TM, Nickenig G, Pedrazzini G, Pozzoli A, Praz F, Puri R, Rodés-Cabau J, Rommel KP, Schäfer U, Schofer J, Sievert H, Tang GHL, Thiele H, Unterhuber M, Vahanian A, von Bardeleben RS, von Roeder M, Webb JG, Weber M, Wild MG, Windecker S, Zuber M, Hausleiter J, Maisano F, Leon MB, Hahn RT, Lauten A, Taramasso M, Lurz P. Outcomes of transcatheter tricuspid valve intervention by right ventricular function: a multicentre propensity-matched analysis. *EuroIntervention.* 2021;17:e343-52.

5. Muntané-Carol G, Taramasso M, Miura M, Gavazzoni M, Pozzoli A, Alessandrini H, Latib A, Attinger-Toller A, Biasco L, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Lubos E, Ludwig S, Kalbacher D, Estevez-Loureiro R, Fam N, Frerker C, Ho E, Juliard JM, Kaple R, Kodali S, Kreidel F, Harr C, Lauten A, Lurz J, Monivas V, Mehr M, Nazif T, Nickening G, Pedrazzini G, Philippon F, Praz F, Puri R, Schäfer U, Schofer J, Sievert H, Tang GHL, Khattab AA, Andreas M, Russo M, Thiele H, Unterhuber M, Himbert D, Urena M, von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Hausleiter J, Lurz P, Maisano F, Leon MB, Hahn RT, Rodés-Cabau J. Transcatheter Tricuspid Valve Intervention in Patients With Right Ventricular Dysfunction or Pulmonary Hypertension: Insights From the TriValve Registry. *Circ Cardiovasc Interv.* 2021;14:e009685.

6. Stocker TJ, Hertell H, Orban M, Braun D, Rommel KP, Ruf T, Ong G, Nabauer M, Deseive S, Fam N, von Bardeleben RS, Thiele H, Massberg S, Lurz P, Hausleiter J. Cardiopulmonary Hemodynamic Profile Predicts Mortality After Transcatheter Tricuspid Valve Repair in Chronic Heart Failure. *JACC Cardiovasc Interv.* 2021;14:29-38.

7. Sorajja P, Whisenant B, Hamid N, Naik H, Makkar R, Tadros P, Price MJ, Singh G, Fam N, Kar S, Schwartz JG, Mehta S, Bae R, Sekaran N, Warner T, Makar M, Zorn G, Spinner EM, Trusty PM, Benza R, Jorde U, McCarthy P, Thourani V, Tang GHL, Hahn RT, Adams DH; TRILUMINATE Pivotal Investigators. Transcatheter Repair for Patients with Tricuspid Regurgitation. *N Engl J Med.* 2023;388:1833-42.

8. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *EuroIntervention.* 2022;17:e1126-96.

9. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter J, Ho E, Juliard JM, Kaple R, Besler C, Kodali S, Kreidel F, Kuck KH, Latib A, Lauten A, Monivas V, Mehr M, Muntané-Carol G, Nazif T, Nickening G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodés-Cabau J, Schäfer U, Schofer J, Sievert H, Tang GHL, Thiele H, Topilsky Y, Rommel KP, Delgado V, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Hahn RT, Bax JJ, Enriquez-Sarano M, Maisano F. Transcatheter Versus Medical Treatment of Patients With Symptomatic Severe Tricuspid Regurgitation. *J Am Coll Cardiol.* 2019;74:2998-3008.