JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2024

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Understanding Tricuspid Regurgitation Regression May Be the Key to Progression of the Field*

Rebecca T. Hahn, MD

Tricuspid regurgitation (TR) is a progressive disease,[1] and increasing severity of TR is associated with increasing mortality and morbidity.[2] Several retrospective studies have identified predictors of TR progression that characterize a population at higher risk of adverse outcomes and who deserve closer observation or possibly earlier intervention. Mutlak et al[3] performed a retrospective cohort study of 1,552 patients with an index transthoracic echocardiogram (TTE) demonstrating trivial or mild TR and determined risk factors for progression to moderate or severe TR. Progression occurred in approximately 19% of patients during a median follow-up of 38 months with independent predictors, including age, female sex, heart failure (HF), pacemaker electrode, atrial fibrillation (AF), and indicators of left heart disease, including left atrial enlargement, elevated pulmonary artery systolic pressure, and left-sided valvular disease. The 4 strongest predictors were pulmonary artery systolic pressure of ≥36 mm Hg, left atrial enlargement, age ≥60 years, and AF. In the absence of any risk factors, the risk of progression was low.

Prihadi et al[4] performed a single-site retrospective analysis of risk factors influencing the time interval for development of moderate or severe TR. They divided 1,000 patients into quartiles of temporal development of significant TR. Risk factors for rapid development included baseline age (OR: 1.02), presence of pacemaker and defibrillator lead (OR: 1.59), presence of mild (vs none) TR (OR: 8.96), tricuspid annulus plane systolic excursion (OR: 0.86), and tricuspid annulus dilation (OR: 1.06). Patients with rapid TR development (≤1.2 years) showed worse outcomes than patients with slower development, and the time to development of TR was associated with all-cause mortality (HR: 1.09 [95% CI: 1.06-1011]; $P < 0.001$).

Bannehr et al[5] performed quantitative TTE measures of TR severity in 1,650 consecutive patients; 14.1% of patients had no TR, 63.8% had mild TR, 17.4% had moderate TR, and 4.7% had severe TR. They found progression of TR (≥1 grade) occurred in 28.4% of patients within the mean study period (1,090 days).[5] Moderate and severe TR (the latter grade included severe, massive and torrential disease), pulmonary artery systolic pressure and impaired right ventricular (RV) function were independent predictors for survival. Overall progression of TR on follow-up was 28.4% and TR progression showed significantly worse survival (HR: 1.44 [95% CI: 1.11-1.81]; $P = 0.006$).

In the observational study by Arteagoitia Bolumburu et al[6] in this issue of *JACC: Cardiovascular Imaging*, 1,843 patients from 9 institutions with at least moderate TR and with a minimum follow-up period of 2 years were prospectively followed with consecutive TTE studies and/or clinical evaluation. At a median follow-up of 2.3 years, 19% of patients had progression of TR. Importantly, the longer the follow-up duration from the time of initial moderate TR diagnosis, the more rapid the progression: 4.9% at 1 year, 10.1% at 2 years, and 24.8% at 3 years.

Predictors of TR progression in the current study included older age (HR: 1.03), lower body mass index (HR: 0.95), chronic kidney disease (CKD) (HR: 1.55), worse NYHA functional class (HR: 1.52), and RV dilation (HR: 1.33). Whether CKD and RV dilatation are

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the Columbia University Irving Medical Center, New York, New York, USA; and the Cardiovascular Research Foundation, New York, New York, USA.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2023.11.016

causal or resultant is difficult to know. Nonetheless, TR progression was associated with right heart chamber dilation, as well as a decrease in ventriculoarterial (RV-PA) coupling and left ventricular ejection fraction (LVEF) ($P < 0.001$). TR progression is associated with an increased cardiovascular mortality and HF hospitalizations (36.7%) compared with regression or nonprogression (23.1% or 24.2%; $P < 0.001$).

There are some conclusions from this observational prospective study that require equipoise. Although progression was associated with a 1.9% ± 12.1% decrease in LVEF, progressors had the highest baseline EF values (58.7% ± 12.1%; $P > 0.001$) compared with nonprogressors or regressors. Interestingly, there was no association between disease severity or progression with tricuspid annular dimensions raising questions about guideline recommendations to intervene with progressive TR in the presence of annular dilatation. The authors do provide further proof that severe TR (HR: 1.66; 95% CI: 0.98-2.81) and massive/torrential TR (HR: 3.80; 95% CI: 1.58-9.11) are associated with increased cardiovascular mortality.

There are multiple additional questions that could be answered with the current study cohort. In the setting of a low incidence of AF (only 50%), the increase in left atrial volume ($P = 0.024$) and smaller LV volumes ($P < 0.05$) associated with increasing severity of TR, along with the association of smaller LV volumes and higher LV ejection fraction (58.7% ± 12.1%) with progression of disease ($P < 0.05$ for all), suggests the possible influence of HF with preserved ejection fraction (HFpEF) on both the severity and progression of TR. HFpEF is also associated with increasing RA size[7] and the current study shows an association with RA area with TR severity and progression ($P < 0.01$ for both). Considering the growing evidence for the association between TR and HFpEF,[7-9] assessing this entity would be an important additional analysis.

Perhaps the most important and unique finding from this large prospective study, is that the number of patients with regression of their TR (n = 361) was twice those progressing (n = 181). The regression and progression groups were not statistically compared however patients who had regression were numerically younger (73.8 ± 11.6 years vs 77.5 ± 10.8 years) with a lower prevalence of women (61% vs 77%), AF (46% vs 55%), and CKD (30% vs 46%); more severe TR by vena contracta width (6.8 ± 3.5 mm vs 6.0 ± 3.5 mm); smaller RA area (24.2 ± 9.0 cm^2 vs 26.1 ± 10.1 cm^2); higher RV-PA coupling (47 ± 0.2 mm/mm Hg vs 44 ± 0.2 mm/mm Hg); and larger LV volumes with a lower LVEF (55.6% ± 14.5% vs 58.7% ± 12.1%). These patients thus could be more representative of patients with ventricular secondary TR. Regression in 38% of patients likely contributed significantly to the absence of progression in the whole cohort over the >2-year follow-up period.

Could regression of TR in the medically-treated cohort of the Triluminate Pivotal Study[10] help explain the outcomes of that randomized controlled trial? Recent analysis of the device arm of the trial suggests that for every 1-grade improvement in TR there is 4.1-point increase in Kansas City Quality of Life Questionnaire Overall Score.[11] The 37.2% of medically treated patients in this trial who exhibited a ≥10-point increase in Kansas City Quality of Life Questionnaire Overall Score at the 1-year follow-up (**Figure 1**) could have had a 2-grade regression of TR over the 1-year follow-up period. Regression of TR in the medical therapy cohort may have affected the ability of that trial to show a mortality or HF hospitalization benefit with interventional therapy.

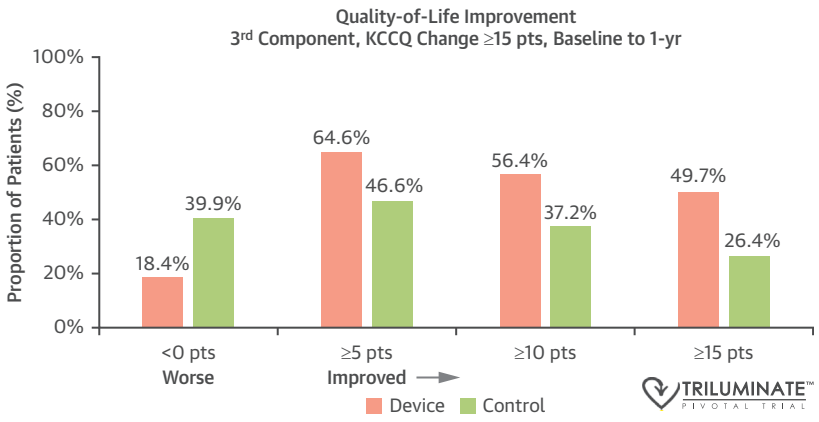
Essential questions for the field which require further study include:

1) What are the clinical, hemodynamic, and echocardiographic predictors of TR regression?
2) Can we identify appropriate medical therapies to effect TR regression?
3) Is regression of TR associated with improvement in outcomes?

Answering these questions will affect daily management decisions but also future trial design. Current guidelines have no class I medical therapies for treatment of TR and understanding how patients with moderate or severe TR were managed may help to support a change in these recommendations. Given the association of increasing severity of TR with worse outcomes, regression of TR would likely positively affect outcomes.

The authors are to be congratulated on the large cohort and prospective nature of this observational study. Their findings add significantly to the literature, highlighting the adverse outcomes associated with progression of TR. The disappointing rate of intervention, which may impact the high mortality and hospitalization rates, is another important observation. The increasing rates of progression with every subsequent year of follow-up support the authors' recommendations to follow moderate TR patients with serial echocardiograms every 1 to 2 years. However, the most interesting finding is the large number of patients that experienced regression of TR. Future research must include a study of these patients, including clinical, echocardiographic, and

FIGURE 1 **ACC.23/WCC Presentation Slides**



Pivotal: A Landmark Randomized Clinical Trial Of Transcatheter Tricuspid Valve Edge-to-Edge Repair For Tricuspid Regurgitation (TRILUMINATE) (accessed October 23, 2023). The significant number of patients in the medical treatment cohort who experienced improvements in quality of life, may represent patients who have regression of the disease. ACC = American College of Cardiology; WCC = World Congress of Cardiology.

hemodynamic predictors, as well as possible contributing medical therapies. Understanding which patients regress and which progress will not only allow us to more effectively manage our patients, but also allow us to design more robust clinical trials for transcatheter tricuspid valve interventions.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Hahn has received speaker fees from Abbott Structural, Baylis Medical, Edwards Lifesciences, Medtronic, Philips Healthcare, and Siemens Healthineers; has institutional consulting contracts for which she receives no direct compensation with Abbott Structural, Anteris, Edwards Lifesciences, Medtronic, and Novartis; and is the Chief Scientific Officer of the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored valve trials, for which she receive no direct industry compensation.

ADDRESS FOR CORRESPONDENCE: Dr Rebecca T. Hahn, Columbia University Medical Center-New York Presbyterian Hospital, Herbert Irving Pavilion, 161 Fort Washington Avenue, New York, New York 10032, USA. E-mail: rth2@cumc.columbia.edu.

REFERENCES

1. Hahn RT. Tricuspid regurgitation. *N Engl J Med*. 2023;388:1876-1891.

2. Hahn RT, Brener MI, Cox ZL, Pinney S, Lindenfeld J. Tricuspid regurgitation management for heart failure. *J Am Coll Cardiol HF*. 2023;11:1084-1102.

3. Mutlak D, Khalil J, Lessick J, Kehat I, Agmon Y, Aronson D. Risk factors for the development of functional tricuspid regurgitation and their population-attributable fractions. *J Am Coll Cardiol Img*. 2020;13:1643-1651.

4. Prihadi EA, van der Bijl P, Gursoy E, et al. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. *Eur Heart J*. 2018;39:3574-3581.

5. Bannehr M, Edlinger CR, Kahn U, et al. Natural course of tricuspid regurgitation and prognostic implications. *Open Heart*. 2021;8.

6. Arteagoitia Bolumburu A, Monteagudo Ruiz JM, Mahia P, et al. Determinants of tricuspid regurgitation progression and its implications for adequate management. *J Am Coll Cardiol Img*. 2024;X:XX-XX. https://doi.org/10.1016/j.jcmg.2023.10.006

7. Harada T, Obokata M, Omote K, et al. Functional tricuspid regurgitation and right atrial remodeling in heart failure with preserved ejection fraction. *Am J Cardiol*. 2022;162:129-135.

8. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart failure with preserved ejection fraction: JACC scientific statement. *J Am Coll Cardiol*. 2023;81:1810-1834.

9. Baratto C, Caravita S, Corbetta G, et al. Impact of severe secondary tricuspid regurgitation on rest and exercise hemodynamics of patients with heart failure and a preserved left ventricular ejection fraction. *Front Cardiovasc Med*. 2023;10:1061118.

10. Sorajja P, Whisenant B, Hamid N, et al. Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med*. 2023;388:1833-1842.

11. Arnold SV, Goates S, Sorajja P, et al. Health status after transcatheter tricuspid-valve repair in patients with severe tricuspid regurgitation: results from the TRILUMINATE pivotal trial. *J Am Coll Cardiol*. 2024;83:1-13.

KEY WORDS regurgitation progression, regurgitation regression, tricuspid regurgitation