ISSN 2666-0873

LETTERS TO THE EDITOR

Dual Aortic Stenosis and Transthyretin Cardiac Amyloidosis

Do We Have Enough Evidence?

We have read and studied the important original article published by Singal et al[1] in *JACC CardioOncology*. Singal et al[1] have advised screening for all severe aortic stenosis (AS) patients especially in those with red flag signs, with an appropriate diagnostic work-up including the exclusion of primary light-chain abnormality and use of ^{99m}Tc pyrophosphate scans.

However, in this study, there was no significant mortality difference between patients in myocardial transthyretin cardiac amyloidosis (ATTR-CA)-negative and -positive groups (3% vs 33%; $P = 0.477$). In order to diagnose 9% of the dual AS+myocardial ATTR-CA patients, the remaining 91% of patients would have to undergo a 99m-technetium pyrophosphate scan.[1] As per our experience, advanced nuclear scan facilities in India are available at a limited number of large, public research hospitals. Advising nuclear scans for all severe AS patients leads to a significant delay in the aortic valve replacement (AVR), increased treatment cost, and mortality. In this study, 15.3% (n = 4 of 26) patients died before AVR and 19.2% (n = 5 of 26) of patients were lost to follow-up. If we assume that all those patients died, then there was a ~35% increase in mortality with a marginal 9% additional diagnosis of dual AS+myocardial ATTR-CA. In our view, Singal et al[1] could have considered univariable association models to determine the risk according to the 2 groups.

Rapezzi et al[2] observed in a multivariable analysis that in patients with untreated amyloidosis, the presence of a hereditary, TTR-related form (mutant ATTR) of CA was associated with good survival; however, patients with wild-type TTR-related amyloidosis were free from major adverse cardiac events. In that study, the 2- and 5-year survival in TTR amyloidosis was 98% and 75%, respectively.[2] TTR amyloidosis may not have been the only cause of death seen in dual AS+myocardial ATTR-CA patients (33%) in this study. Singal et al[1] suggest that the reason for the positive scan is high myocardial involvement in one statement; however, in another statement, they suggest that the negative myocardial biopsy may be caused by low myocardial involvement. In our view, these statements are contradictory to each other and need further clarification. Singal et al[1] stated that "Patients with the dual disease should be monitored closely even after AVR, considering the trend toward worse post-AVR survival seen in many studies." However, there was no significant difference in mortality between the 2 groups in Singal et al study.

*Praveen K. Gupta, DM

*Department of Cardiology
Praveen Heart Clinic and Research Foundation
New Delhi 110092, India
E-mail: praveenkumargupta2002@gmail.com

https://dx.doi.org/10.1016/j.jaccao.2021.10.003

The author has reported that they have no relationships relevant to the contents of this paper to disclose.
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.

REFERENCES

1. Singal AK, Bansal R, Singh A, et al. Concomitant transthyretin amyloidosis and severe aortic stenosis in elderly Indian population. *J Am Coll Cardiol CardioOnc*. 2021;3(4):565-576.

2. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation*. 2009;120(13):1203-1212.

REPLY: Dual Aortic Stenosis and Transthyretin Cardiac Amyloidosis: Do We Have Enough Evidence?

We acknowledge Dr Gupta's concerns regarding mortality differences between patients with lone aortic stenosis (AS) versus those with both AS and transthyretin cardiac amyloidosis (ATTR-CA), as well as the results and utility of 99m-technetium pyrophosphate (PYP) scan.

Before designing studies to understand ATTR-CA's mortality impact (requiring much larger sample

sizes), it was pertinent to first establish that ATTR-CA occurs in significant numbers in the target demographic profile. ATTR-CA epidemiology has ethnic variations, but no study had previously looked at ATTR-CA in India. Therefore, we conducted this pilot study primarily to understand the ATTR-CA prevalence among Indian patients with severe AS.[1] Our exploratory study was not designed to detect mortality differences, but rather to be used as foundation for further research in amyloid cardiomyopathy in the Indian subcontinent. Statistical modeling including Cox regression analysis was not performed because this type of analysis would be underpowered, caused by the small number of deaths (n = 2). There are still questions regarding the long-term prognosis of dual disease. Many studies (eg, references 5, 8, and 25 in our paper) as well as a recent meta-analysis suggest lower survival rates in dual disease.[2]

We agree with Dr Gupta's view regarding limited nuclear scan facilities in India. Hence, we suggested consideration of a PYP scan not in all severe AS patients, but rather only in those with "red flags." This strategy would limit the number of patients requiring this test. Also, PYP scans can be performed postoperatively; thus, aortic valve replacement need not be delayed while awaiting the scan. Moreover, we believe that limited availability of scan facilities should not be the primary deterrent for advanced research in this relatively unexplored disease, especially when the potential disease burden is high. Rather, such important research should invigorate more widespread availability and appropriate utilization of these scans.

The suggested contradiction in statements regarding ATTR myocardial burden is readily resolved when each statement is independently juxtaposed against the relevant context. Low myocardial burden as a possible reason for negative biopsies was in reference to other studies in which the mean age of the recruited population was ~80 years (10 years older than ours). Because TTR is a progressive disease whose prevalence increases with age, TTR burden would likely be even higher if our study subjects were studied a decade later. This does not negate the fact that ATTR myocardial burden at the time of our study was high enough for the PYP scan to be positive.

Finally, the landscape of ATTR-CA diagnosis and treatment has changed remarkably since an early report in 2009, when the paper by Rapezzi et al[3] regarding prognosis of ATTR-CA was published. The same group now believes that ATTR-CA is not an innocent bystander and suggests medical therapy for amyloidosis in addition to aortic valve replacement in dual disease.[4] This is important given the progressive nature of ATTR-CA and associations with poor quality of life.[5]

Aayush Kumar Singal, MD, DM
Avinainder Singh, MD, MMSc
Raghav Bansal, MD, DM
***Sundeep Mishra, MD, DM**

*Department of Cardiology
CN Centre
All India Institute of Medical Sciences, 7th Floor
New Delhi 110029, India
E-mail: drsundeepmishranic@gmail.com

https://dx.doi.org/10.1016/j.jaccao.2022.02.005

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

1. Singal AK, Bansal R, Singh A, et al. Concomitant transthyretin amyloidosis and severeaortic stenosis in elderly Indian population: a pilot study. *J Am Coll Cardiol CardioOnc*. 2021;3(4):565–576.

2. Sin-Ying Ho J, Kor Q, et al. Prevalence and outcomes of concomitant cardiac amyloidosis and aortic stenosis: A systematic review and meta-analysis. *Hellenic J Cardiol*. Published online November 29, 2021. https://doi.org/10.1016/j.hjc.2021.11.001

3. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation*. 2009;120(13):1203–1212.

4. Fabbri G, Serenelli M, Cantone A, et al. Transthyretin amyloidosis in aortic stenosis: clinical and therapeutic implications. *Eur Heart J Suppl*. 2021;23(Supplement_E):E128–E132.

5. Lane T, Fontana M, Martinez-Naharro A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation*. 2019;140(1):16–26. https://doi.org/10.1161/CIRCULATIONAHA.118.038169