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Aortic Stenosis, Left Ventricular Remodeling, and Renin-Angiotensin System Blockade

Mindelsohn Way
Birmingham, B15 2TH
United Kingdom
E-mail: adnan.nadir@uhb.nhs.uk

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I read the paper by Treibel et al. (1) with great interest. In this elegant study, the authors showed that in patients with aortic stenosis (AS) who had undergone surgical aortic valve replacement, the diffuse fibrosis and myocardial cellular hypertrophy regress with time and that regression is accompanied by structural and functional improvements.

There is increasing appreciation that AS incorporates a disease process that extends beyond the stenotic valve itself, leading to an aortic valvular "heart" disease (2,3). The increasing afterload forces the myocardium to remodel and become hypertrophied in an effort to maintain adequate cardiac output and systolic function. These changes are characterized by cardiomyocyte hypertrophy and extracellular matrix expansion (3).

The renin-angiotensin system has a major influence on myocardial physiology, and there is some evidence for this influence in AS: it regulates the degree of left ventricular hypertrophy and the extent of fibrosis in the myocardium (2,3). Renin-angiotensin system inhibitors reduce left ventricular hypertrophy independent of blood pressure and can reduce the extent of myocardial fibrosis. This reduction, in turn, has a positive influence on future cardiovascular events, including in patients with AS (2,4,5).

In the present study (1), nearly one-half of the patients were taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). It would be intriguing to see if the authors could stratify the data according to the use of ACE inhibitors/ARBs and explore the regression of myocardial cellular hypertrophy and myocardial fibrosis. It is plausible that use of ACE inhibitors/ARBs had a positive impact on regression myocardial cellular hypertrophy and myocardial fibrosis and that among patients taking ACE inhibitors/ARBs, the regression may have been more pronounced (2,4,5).

*M. Adnan Nadir, MD

*Department of Cardiology
Queen Elizabeth Hospital
University of Birmingham

REPLY: Aortic Stenosis, Left Ventricular Remodeling, and Renin-Angiotensin System Blockade

We thank Dr. Nadir for his interest in RELIEF-AS (Regression of Myocardial Fibrosis After Aortic Valve Replacement) (1) and the potential impact of the renin-angiotensin system (RAS) on myocardial remodeling. Dr. Nadir postulates that RAS inhibition may accelerate regression of myocardial cellular hypertrophy and fibrosis. We know that RAS inhibition (by angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) achieves this regression in hypertension, with further support from the RIAS (Ramipril In Aortic Stenosis) trial of moderate to severe aortic stenosis (2). In this study, ramipril led to a modest but progressive reduction in left ventricular mass (LVM) but with no significant changes in myocardial functional indices.

In RELIEF-AS, RAS inhibition was not predictive of cell or matrix regression at 1-year post-intervention (see Online Appendix of Treibel et al. [1]). Neither were other data stratifications (sex, presence or absence of hypertension, coronary artery disease, diabetes, or baseline pattern/burden of hypertrophy) predictive. The multivariable predictors of matrix regression at baseline were indexed LVM, N-terminal pro-B-type natriuretic peptide level (as a marker of left ventricular distress), and the extracellular volume fraction.

Why did RAS inhibition not accelerate regression in the RELIEF-AS study (1)? First, the magnitude of afterload reduction by surgical aortic valve replacement may swamp any signal: mean valve gradients decreased from 48 ± 16 mm Hg to 12 ± 6 mm Hg with 19% LVM regression at 1 year, compared with the LVM regression in the RIAS trial (2) of 2.5% at 1 year (or 5.4% compared with their placebo control group). Second, although RAS inhibition reduces LVH across various diseases (the majority of evidence is in arterial hypertension), aortic stenosis is different: the pressure drop is pre-coronary, and there are clear differences in the myocardial changes in aortic stenosis compared with those in hypertension (3). Third, LVH needs to be considered in context. Not all LVH is bad: few would consider the physiological hypertrophy of athletes (predominantly cellular hypertrophy) as a potential drug target, and in moderate aortic stenosis (the RIAS study), at least some of the LVH may have been appropriate (4). The imaging techniques used in RELIEF-AS in differentiating cellular and matrix responses within LVH may offer us new understanding. At this time, we do not know the relative effects of different drugs on myocyte hypertrophy versus interstitial expansion; future care may deliver personalized medicine approaches based on the precise type and context of any LVH to maximize outcome improvement.

Begoña Lopez, PhD
Arantxa Gonzalez, PhD
Javier Díez, MD, PhD
James C. Moon, MD
***Thomas A. Treibel, PhD**

*Barts Heart Centre
St. Bartholomew's Hospital
2nd Floor, King George V Block
London EC1A 7BE
United Kingdom
E-mail: thomas.treibel@bartshealth.nhs.uk

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Revascularization Strategies in Patients With Acute MI and Cardiogenic Shock

In a recent issue of the *Journal*, Lee et al. (1) present data based on the Korea Acute Myocardial Infarction Registry (KAMIR)-National Institutes of Health registry and conclude that multivessel percutaneous coronary intervention (PCI) is associated with a lower risk of death in ST-segment elevation myocardial infarction and cardiogenic shock (CS) compared with infarct-related-artery (IRA)-only PCI.

We believe that the following points warrant more detailed discussion:

- It remains unclear if and how patients were prospectively assigned to multivessel PCI. For example, patients in whom death occurred before staged procedures seem to have been included in the IRA-only PCI group. Statistical adjustment for this confounder is not possible. This factor could be a major trigger for the higher mortality after IRA-only PCI.
- The reported 1-year mortality (27%) and the rate of renal replacement therapy at 30 days (3%) are extremely low for a CS cohort.
- There have been recent reports on the current topic based on the KAMIR registry (2,3). The findings are inconsistent despite overlapping patient inclusion, similar definitions, and comparable baseline characteristics, which could be indicative of unknown confounders triggering the differing results.
- The CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial showed superiority of culprit-lesion-only PCI with the option of staged revascularization over immediate multivessel PCI with respect to all-cause mortality (4). The authors repeatedly state that "…patients with CS were excluded in all randomized trials…"; this statement is misleading. Furthermore, in the present analysis (1), 40% of the so-called multivessel PCI group underwent staged procedures. This total reflects the IRA-only PCI with possible staged revascularization arm of the CULPRIT-SHOCK