Meta-Analysis for the Use of Renin-Angiotensin Inhibitors in Post-TAVR Patients

Transcatheter aortic valve replacement (TAVR) has revolutionized the management of patients with symptomatic severe aortic stenosis (AS). With the recent favorable results of TAVR in the low surgical-risk population, it is expected to become the preferred choice for valve replacement in AS, irrespective of surgical risk.[1] However, we have a paucity of data for the postprocedural management of these patients. Approximately 50% of patients after TAVR die within 5 years of their procedure.[2] Renin-angiotensin inhibitors (RAI), with their favorable effects on ventricular remodeling and associated survival benefits in AS patients have been touted to reduce morbidity and mortality in this population, although data from randomized trials are not yet available. Given there are no current recommendations regarding the use of RAI post-TAVR, our analysis aims to collate the current evidence from observational data regarding the effects of RAI in patients post-TAVR.

We performed a literature search in PubMed, Embase, and Cochrane Central from inception through July 29, 2019. Reference list of relevant articles and also the conference proceedings were searched as well to ensure completeness. The keywords including ''Renin-Angiotensin Inhibitor'' OR ''angiotensin receptor blocker'' (ARB) OR ''angiotensin-converting enzyme inhibitor'' (ACEi) AND ''transcatheter aortic valve replacement'' OR ''transcatheter aortic valve implantation,'' were utilized with human limits activated. No language or publication year restrictions were used. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines throughout all the stages of design and implementation. Two independent authors screened the studies to identify the appropriate, relevant articles. The articles were considered for inclusion if they had the comparative data available for with or without the use of ACEi or ARB in AS patients who underwent TAVR. The primary outcome of interest was all-cause mortality. The odds ratios (OR) or hazard ratios with their corresponding confidence intervals (CIs), from propensity score matching whenever available or from adjusted multivariate analysis when propensity score matching was not available, were used to calculate the relative treatment effects and standard errors. Logarithmic values were used to decrease the variance for meta-analysis. The Review Manager (RevMan) computer software [version 5.3]; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, was used to perform the Mantel-Haenszel generic inverse variance meta-analysis. A two-sided p-value <0.05 was considered to represent statistical significance.

Our initial search yielded 336 articles. After electronic and manual deduplication and removal of irrelevant articles after the title and abstract screening, 18 articles were pulled for full-text review. In the end, 3 studies were identified to have relevant data for quantitative meta-analysis.[3-5] Our results showed that the use of RAI after TAVR was associated with a 14% reduction in all-cause mortality (OR 0.86; 95% CI 0.79 to 0.94; p-value = 0.001; $I^2 = 44\%$; see Figure 1). A small number of studies precluded subgroup and any further analyses. The mean follow-up was 2 years suggesting that these effects of improved mortality persisted with a mid-term benefit.

The significant finding of our analysis is that RAI is associated with a statistically significant improvement in all-cause survival in patients after TAVR. RAI has the potential to attenuate cardiac remodeling through multiple mechanisms. In AS, persistently elevated pressures lead to left ventricular (LV) dysfunction and myocardial hypertrophy. RAI has been beneficial in hypertensive patients by reducing LV hypertrophy. An earlier randomized trial found that RAI independently regressed LV mass and hypertrophy at 1 year.[2]

Furthermore, in patients post-AVR, the fibrotic changes may become irreversible in 1 year. Previous work has also demonstrated that myocardial fibrosis may even be triggered by angiotensin II. These fibrotic changes may have deleterious effects on cardiovascular morbidity and overall mortality—all this point toward a theoretical benefit of RAI in patients post-TAVR. [2]

The studies included in our analyses have shown beneficial effects of RAI in secondary outcomes, including reduced heart failure hospitalization and cardiovascular mortality. Although our findings support the use of RAI after TAVR, the potential for side effects, pill burden, and comorbidities, including chronic kidney disease is real. Also, this meta-analysis is based on observational data. Although the covariates were appropriately matched and adjusted for, the unaccounted confounders remain a possibility, making our findings more hypothesis-generating. Therefore, these results should be interpreted with caution as they cannot confer causality because of the lack of randomization. However, these findings are significant, and the current analysis is based upon the best available evidence. The results of the dedicated open-label randomized trial RASTAVI (Renin-angiotensin System Blockade Benefits in Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation)

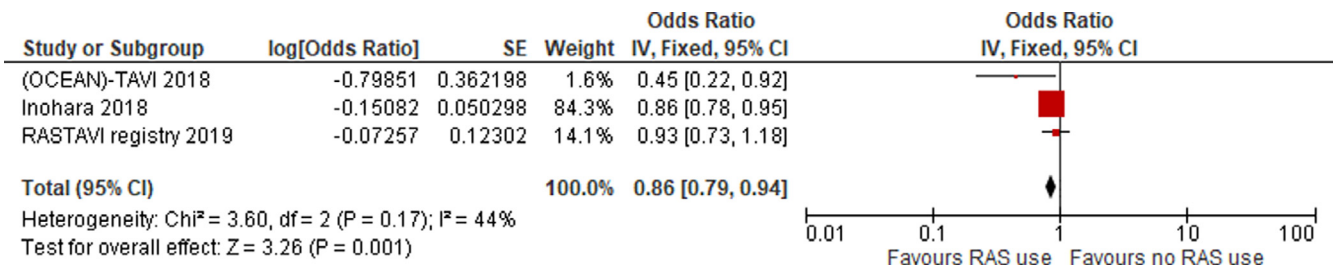

Figure 1. Effect of renin-angiotensin inhibitors after TAVR on all-cause mortality. OCEAN-TAVI = Optimized CathEter vAlvular iNtervention Transcatheter Aortic Valve Implantation; RASTAVI = Renin-angiotensin System Blockade Benefits in Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation; SE = standard error; IV = inverse variance.

should clarify the pharmacological guidance in these patients.

Disclosure

None of the authors has any relevant disclosures.

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