CONTEMPORARY REVIEW

Renin-Angiotensin System Blockade in Aortic Stenosis: Implications Before and After Aortic Valve Replacement

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ABSTRACT: Aortic stenosis (AS) is a common valvular heart disease in the aging population that is characterized by a variable period of asymptomatic phase before development of symptoms and severe AS. Mortality and morbidity is substantial even after aortic valve replacement, in part related to persistent left ventricular hypertrophy, diastolic dysfunction, and heart failure. Renin-angiotensin system (RAS) blockade therapy is associated with modulation of adverse left ventricular remodeling, reduction in myocardial hypertrophy, and fibrosis, resulting in clinical improvements in patients with congestive heart failure. There are emerging data to suggest benefit associated with RAS blockade in patients with AS before and after AVR with regard to potentially slower progression of aortic valve calcification, left ventricular mass and survival benefit in favor of RAS blockade group before AVR, and also survival benefit in patients after AVR. We review the available data to understand the role of RAS blockade before AVR and in patients undergoing surgical AVR and transcatheter AVR. There are significant survival advantages of RAS inhibition in patients with AS undergoing surgical AVR or transcatheter AVR. On the basis of existing literature, adequately powered randomized trials are needed to evaluate the role of RAS inhibition in patients with AS.

Key Words: aortic stenosis ■ aortic valve replacement ■ renin-angiotensin system ■ transcatheter aortic valve replacement

Aortic valve disease is a common valvular heart disease in the aging population.1 It is estimated that >5% of adults >75 years of age are affected by aortic stenosis (AS).2 Treatment of severe symptomatic aortic valve disease is aortic valve replacement, surgical or transcatheter, depending on patient risk profile. Aortic sclerosis is a precursor to AS and is characterized by changes in valve leaflet morphology without obstruction. There is usually a variable-period asymptomatic phase before development of symptoms and severe AS. Mortality and morbidity are substantial even after AVR, including heart failure hospitalizations and adverse cardiovascular events.3,4 Renin-angiotensin system (RAS) blockade therapy is associated with modulation of adverse left ventricular (LV) remodeling, reduction in myocardial hypertrophy, and fibrosis, resulting in clinical improvements in patients with congestive heart failure.5–7 There are emerging data to suggest benefit associated with RAS blockade in patients with aortic valve disease before and after AVR. We reviewed the available published data to understand (1) the role of RAS blockade in patients with aortic valve disease before AVR; (2) the role of RAS blockade in patients undergoing surgical aortic valve replacement (SAVR); and (3) the role of RAS blockade in patients undergoing transcatheter aortic valve replacement (TAVR).

ROLE OF RAS BLOCKADE ON AORTIC VALVE AND LV PATHOPHYSIOLOGY

Calcific or senile AS is usually preceded by variable period of progressive aortic sclerosis. In a large population-based prospective study consisting of
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Role of RAS Blockade on Progression of AS

Inflammation is the first step in development of AS. A normal aortic valve has almost no inflammatory cells, whereas a stenotic valve has progressive recruitment of macrophages, T lymphocytes, and mast cells, which are capable of secreting proinflammatory cytokines (Figure 1). The second step is lipid accumulation. Oxidized low-density lipoprotein has been found to colocalize with T lymphocytes and calcium deposits in stenotic aortic valves. Animal studies have confirmed experimental hypercholesterolemia-induced thickening and stenosis of the aortic valve. Normal aortic valves are avascular; however, stenotic aortic valves are associated with neovascularization, which likely facilitates migration of inflammatory cells and lipids into the leaflets. This is followed by calcification and ossification mediated by osteoblasts and regulators of calcification such as osteopontin, osteocalcin, osteonectin, and so on. Angiotensin II, the enzymatic product of ACE is expressed in atherosclerotic plaques. Using applied immunohistochemical techniques, ACE and angiotensin II have been shown to be present in sclerotic and stenotic aortic valves, but not in normal aortic valves. Based on the observation of association of ACE with low-density lipoprotein in both lesions and plasma, it has been suggested that ACE may enter the stenotic valve lesions from the circulation bound to and carried by low-density lipoprotein particles. Angiotensin II and profibrotic angiotensin II type I receptors were also found in stenotic aortic valves and colocalized with ACE in the lesions. The angiotensin II–forming potential is increased in stenotic aortic valves by way of upregulation of 2 alternative angiotensin II–generating enzymes, chymase and cathepsin G. By way of promoting inflammation and fibrosis, angiotensin II plays an important role in the pathogenesis of AS.

Pharmacologic inhibition of the angiotensin II pathway could potentially lower progression of aortic valve inflammation and calcification (Figure 1, Table 1). In a retrospective observational study, ACE inhibitor (ACEI) use was associated with lower rate of aortic valve calcium accumulation, as assessed by serial electron beam computed tomographic scans. In contrast, another retrospective study did not find a difference in progression of AS with ACEI therapy. It has been suggested that angiotensin receptor blockers (ARBs), which are the final pathway for blockade of effects of angiotensin II may be superior to ACEIs in slowing the progression of AS since there are other angiotensin II–forming enzymes (chymase and cathepsin G) other than ACE. In support of this theory, in a study of hypercholesterolemic rabbits,
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the angiotensin II type I receptor antagonist olmesartan was shown to inhibit atherosclerotic changes and osteoblast transdifferentiation in aortic valves while preserving endothelial integrity. Additional research is required to further understand the mechanism and whether inhibition of RAS slows the progression of AS.

Role of RAS Blockade on LV Function

The second potential mechanism of benefit associated with RAS blockade in AS may be related to effects on LV function (Figure 2). AS is associated with compensatory LVH, and progressive myocardial hypertrophy results in reduced myocardial perfusion, interstitial fibrosis, decline in ventricular function (systolic and diastolic), heart failure, arrhythmogenicity, and sudden death. Data from animal models have shown that ACEI therapy is associated with regression of LVH, improvement in myocardial contractility, and delayed progression to congestive heart failure. Data from patients with heart failure have shown that RAS inhibition with ACEI or ARBs is associated with reduction in LVH and fibrosis, leading to improvement in heart failure, left ventricular ejection fraction (LVEF), and survival. Similarly, data from patients with hypertension have shown that RAS inhibition can lead to regression of myocardial fibrosis and hypertrophy, resulting in improved diastolic function. Clinical data are presented below, evaluating the role of RAS inhibition before and after aortic valve replacement (Figure 3).

CLINICAL DATA ON ROLE OF ACEI/ARB BEFORE AORTIC VALVE REPLACEMENT

A prospective, randomized, double-blind, placebo-controlled trial the ACEI ramipril (RIAS [Ramipril in Aortic Stenosis] trial) was reported recently. In this study, 100 patients with moderate or severe asymptomatic AS were randomized to ramipril 10 mg daily (n=50) or placebo (n=50) for 1 year. Cardiac magnetic resonance imaging, echocardiography, and exercise...
testing were performed at 0, 6, and 12 months. The primary end point studied was reduction in LV mass. Secondary end points included several cardiac magnetic resonance and echocardiographic parameters, blood pressure (BP), B-type natriuretic peptide, and exercise distance. There was a modest but progressive reduction in LV mass in the ramipril group compared with the placebo group (mean change, −3.9 versus +4.5 g; P=0.0057). There were also trends toward improvements in other echocardiographic parameters: preservation of tissue Doppler systolic velocity in ramipril group compared with placebo, and slower rate of progression of AS assessed by direct planimetry on cardiac magnetic resonance imaging.

Table 1. Impact of ACEI/ARB Pre AVR

| First Author (Ref no.) | Study Type | Patient Characteristics | ACEI/ARB Group, n (Intervention) | Non ACEI/ARB Group | Clinical Outcome | Imaging Outcome (Reverse Remodeling, Progression of AS) |
|-----------------------|------------|-------------------------|---------------------------------|---------------------|-----------------|-----------------------------------------------------|
| O'Brien et al21        | Retrospective observational | Asymptomatic patients undergoing at least 2 serial EBCT scans 6 mo apart for the purpose of coronary calcium screening, with AVC score of ≥10 on initial scan | 43                  | 80                  | Not studied     | Unadjusted and adjusted median rates of AVC score change were significantly higher in non-ACEI group than in the ACEI group. Adjusted odds ratio (95% CI) for AVC progression significantly lower in ACEI group (0.29 [0.11–0.75]; P=0.01) |
| Rosenhek et al22       | Retrospective observational | Patients with AS with peak aortic jet velocity >2.5 m/s with ≥2 echocardiographic exams at least 6 mo apart | 102                 | 109                 | Not studied     | No difference in hemodynamic progression of AS in ACEI vs no ACEI group (P=0.29) |
| Bull et al24           | Prospective, randomized, double-blind, placebo-controlled; (RIAS trial) | Moderate or severe asymptomatic AS | 50 (Ramipril 10 mg daily)     | 50 (placebo)        | Not studied     | At 1 y, significant reduction of LV mass (P=0.006), slower progression of AS (P=0.07), preserved tissue Doppler systolic velocity (P<0.04) in the ramipril group compared with placebo |
| Nadir et al25          | Retrospective, population-based, longitudinal cohort study | Patients with AS (Total 2117; mild-moderate AS in 1585, severe AS in 532) | 699                 | 1418                | Not studied     | Greater reduction in SBP (P=0.001) and less progression of LV mass (P=0.04) in ACEI/ARB group |
| Bang et al26           | Retrospective review secondary analysis of patients enrolled in randomized SEAS trial | Asymptomatic mild to moderate AS | 769                 | 1104                | Not studied     | Greater reduction in SBP (P=0.001) and less progression of LV mass (P=0.04) in ACEI/ARB group |
| Goh et al27            | Retrospective observational | Consecutive patients with severe AS, preserved LVEF | 113                 | 315                 | Not studied     | Greater reduction in SBP (P=0.001) and less progression of LV mass (P=0.04) in ACEI/ARB group |
| Capoulade et al28      | Retrospective observational | 338 patients with AS, 4 groups: no hypertension and no RAS blockade (control group), hypertension and no RAS (hypertension group), ACEI group, ARB group | 169                 | 169                 | ARB use associated with slower progression of AS compared with ACEI group and control group | ARB use associated with greater reduction in occurrence of AVR or death (HR, 0.51; 95% CI, 0.28–0.89; P=0.01) compared with hypertension group |

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AS, aortic stenosis; AVC, aortic valve calcium; AVR, aortic valve replacement; EBCT, electron beam computed tomography; HR, hazard ratio; and LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RAS, renin-angiotensin system; RIAS, Ramipril in Aortic Stenosis SBP, systolic blood pressure; SCD, sudden cardiac death; and SEAS, Simvastatin and Ezetimibe in Aortic Stenosis.
imaging (valve area 0.0 cm\(^2\) in Ramipril group versus −0.2 cm\(^2\) in the placebo group; \(P=0.067\)). There was a trend towards stabilization of B-type natriuretic peptide in the Ramipril group (−0.50 pmol/L) and increase in the placebo group (+8.2 pmol/L). There were no significant changes in distance walked on treadmill at 12 months compared with baseline in both groups. The study was too small to evaluate impact on clinical outcomes. The findings of this small but randomized study support the need for a large randomized trial to study the impact of RAS blockade in patients with AS (Table 1).

Nadir et al performed a retrospective study including 2117 patients with AS from an echocardiography database in Scotland to investigate the impact of RAS blockade on outcomes in AS.\(^{25}\) Patients with AS who had at least 2 prescriptions dispensed for ACEI or ARB constituted the ACEI/ARB group (RAS blockade group) and all other patients who were never prescribed an ACEI/ARB formed the control group (no ACEI/ARB). Outcome measures included all-cause mortality and cardiovascular events (cardiovascular death or hospitalizations). The AS was nonsevere (mild to moderate) in 1585 (75%) patients and severe in 532 (25%) patients. A total of 699 patients (33%) received an ACEI or ARB. It is important to note that patients in the ACEI/ARB group had a higher incidence of significant comorbidities such as diabetes mellitus, LV dysfunction, and previous cardiovascular events at baseline, in addition to more patients in this group being prescribed digoxin and oral anticoagulant therapy suggesting underlying atrial fibrillation. Over a mean follow-up period of 4.2 years, patients treated with an ACEI or ARB had significantly lower all-cause mortality with an adjusted hazard ratio (HR) of
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The study population consisted of 1873 patients with aortic stenosis (AS). The study recently evaluated the safety and outcomes of retrospective, nonrandomized data, this large-scale study reflects real-world data and adds to the growing body of evidence suggesting beneficial effects of RAS blockade in patients with AS.

Outcomes were favorable for ACEI/ARB when analysis was stratified on the basis of the severity of AS. The authors concluded that RAS blockade therapy may be associated with less LV pathological remodeling, consistent with some of the other studies discussed above.

A secondary retrospective analysis/substudy from the randomized SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study recently evaluated the safety of RAS blockade with ACEIs or ARBs in patients with AS. The study population consisted of 1873 patients with asymptomatic severe AS and normal LVEF from the SEAS study. Outcomes evaluated include risk of sudden cardiac death, cardiovascular death and all-cause mortality. A total of 769 (41%) patients received RAS blockade therapy with ACEI or ARB. Over a median follow-up of 4.3 years, RAS blockade was not associated with sudden cardiac death, cardiovascular or all-cause mortality compared with the non-RAS blockade group. This was confirmed in propensity-matched analysis. RAS blockade was associated with larger reduction in systolic blood pressure (P=0.001) and less progression of LV mass (15.4±1.2 versus 18.5±1.2 g/m²; P=0.04). This study also adds to the above growing body of evidence that suggests beneficial effects of RAS blockade in patients with AS, in addition to confirming the safety of these agents in this patient population. A systematic review and meta-analysis of 3 randomized controlled trials and 5 observational studies confirmed the safety of RAS blockade in patients with AS with no increase in risk of mortality.

A retrospective study evaluated the impact of RAS blockade on LV remodeling in patients with severe AS and preserved LVEF stratified by normal or low flow (stroke volume index cutoff of 35 mL/m²). Among 426 such patients, 242 (57%) had low flow severe AS and 186 (43%) had normal-flow severe AS. Among the low-flow and normal groups, 64 (26%) and 49 (26%) patients, respectively, were treated with RAS blockade. LV mass index and incidence of concentric LVH were found to be significantly lower in the low-flow severe AS group treated with RAS blockade compared with those not treated with RAS blockade despite higher incidence of diabetes mellitus in the RAS blockade group. Such differences in LV mass and LVH were not observed in the normal-flow patients with severe AS. The authors concluded that RAS blockade therapy may be associated with less LV pathological remodeling, consistent with some of the other studies discussed above.

A retrospective observational study evaluated the impact of hypertension and RAS blockade on progression of AS. Patients with AS (n=338) were divided into 4 groups based on diagnosis of hypertension and use of drugs: (1) control group—no hypertension and no RAS blockade (n=92; 27%), (2) hypertension group—patients with hypertension but no RAS blockade (n=77; 23%), (3) ACEI group—patients treated with ACEI (n=113; 33%), and (4) ARB group—patients treated with ARB (n=56; 17%). Compared with the control group, AS progression rate was significantly faster in the patients in the hypertension group and slower in the ARB group, whereas the progression rate in the ACEI group was similar to the control group. In a multivariate analysis, presence of hypertension remained associated with faster progression of AS, whereas ARB use was associated with slower progression rate. Compared with the hypertension group, the ARB group had a 2-fold reduction in the occurrence of AVR or death (HR, 0.51; 95% CI, 0.28–0.89; P=0.01), while hypertension and ACEI groups remained associated with increased mortality. The authors concluded that hypertension is associated with faster AS progression, and ARBs but not ACEIs were found to be associated with better survival.
**IMPACT OF ACEIS/ARBS IN PATIENTS UNDERGOING SAVR**

Severe AS is associated with LVH and diastolic dysfunction. Studies have shown that LVH can persist after AVR and is associated with worse long-term outcome and mortality.\(^{34-36}\) Data from the PARTNER (Placement of Aortic Transcatheter Valve) trial demonstrate in high-surgical-risk patients with severe LVH undergoing TAVR, those with greater early LV mass regression had one-half the rate of rehospitalization over the subsequent year compared with those with lesser regression.\(^{37}\) Recently, several studies have demonstrated association between RAS blockade therapy and beneficial outcome after SAVR (Table 2).\(^{38-41}\)

A large retrospective cohort study from the Cleveland Clinic was the first study evaluating the role of RAS blockade therapy and outcomes following SAVR for severe AS.\(^{26}\) Patients who were prescribed an ACEI or ARB after SAVR for severe AS between 1991 and 2010, with at least 2 refills 90 days apart and at least a 6-month follow-up (RAS blockade group, n=741) were compared with those who did not receive these prescriptions (non–RAS blockade group, n=1011). The primary outcome was survival rates after SAVR, and secondary end points were changes in LV mass index, LVEF, and left atrial size. The study showed that the overall unadjusted estimated survival rates at 1, 5, and 10 years were significantly greater in the RAS-blockade group than in the non–RAS blockade group (99%, 90%, and 69% versus 99%, 81%, and 53%, respectively; \(P<0.001\)). Among propensity-matched patients, estimated survival at 1, 5, and 10 years remained significantly higher in the RAS group compared with

### Table 2. Impact of ACEI/ARB After AVR

| First Author (Ref no.) | Study Type | First | ACEI/ARB Group | Non-ACEI/ARB Group | Clinical Outcome | Echocardiographic Outcome (Reverse Remodeling) |
|------------------------|------------|-------|----------------|-------------------|-----------------|-----------------------------------------------|
| Goel et al\(^{38}\)    | Retrospective, single-center, post SAVR | 741   | 1011           |                   | In unadjusted and propensity-matched groups, survival was significantly greater in ACEI/ARB group at 1, 5, and 10 y \((P<0.001)\) | For propensity-matched cohort, no significant difference in LVMI \((P=0.37)\), LVEF \((P=0.67)\) or LA size \((P=0.43)\) between the 2 groups |
| Dahl et al\(^{39}\)    | Prospective, randomized, blinded, single-center, post SAVR | 57    | 57             | (candesartan)     | No difference in mortality or hospitalization between groups \((P=0.85)\) | At 12 mo, significantly greater regression of LV mass \((P=0.015)\), decrease in relative wall thickness \((P<0.03)\), greater improvement in longitudinal LV systolic function assessed by mean S’ wave \((P=0.01)\) and greater decrease in LA volume index \((P=0.02)\) in candesartan group |
| Magne et al\(^{40}\)   | Retrospective, single-center, post SAVR | 268   | 240            |                   | Operative mortality lower in ARB group \((P=0.026)\). In unadjusted and propensity matched groups, 8-y survival significantly better in ACEI/ARB group \((P<0.0001)\) | Not studied |
| Yiu et al\(^{41}\)     | Retrospective, single center, post SAVR, MVR | 62    | 88             |                   | At median follow-up of 50 mo, survival significantly better in ACEI/ARB group \((P<0.01)\) | Not studied |
| Ochiai et al\(^{42}\)  | Retrospective, multicenter, post TAVR | 371   | 189            |                   | In unadjusted and propensity-matched groups, 2-y mortality was significantly lower in ACEI/ARB group \((P=0.031\) and \(P=0.025\), respectively) | At 6 mo, ACEI/ARB group had significantly greater LVMI regression \((P=0.024)\) |
| Rodriguez-Gabella et al\(^{43}\) | Retrospective, multicenter, post TAVR | 1622  | 1163           |                   | At 3-y median follow-up, mortality significantly lower in RAS blockade group \((P<0.001)\). Also rates of MI, new-onset AF, stroke, and CHF rehospitalization lower in RAS blockade group | Greater reduction in left ventricular volumes and hypertrophy in RAS group |
| Inohara et al\(^{44}\) | Retrospective cohort study, STS/ACC-TV T registry | 8648  | 12 844         |                   | At 1 y, mortality lower in ACEI/ARB group \((HR, 0.82; 95\% CI, −3.5\% to −1.4\%) and lower CHF readmission rates \((HR, 0.86; 95\% CI, 0.79–0.95)\) | Not studied |
| Chen et al\(^{45}\)    | Retrospective cohort study, PARTNER 2 trial and registries | 1736  | 2243           |                   | At 2 y, all-cause mortality \((18.6\% vs 27.5\%; P<0.0001)\) and cardiovascular mortality \((12.3\% vs 17.9\%; P<0.0001)\) lower in ACEI/ARB group | Not studied\(^{49}\) |

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CHF, congestive heart failure; HR, hazard ratio; LA, left atrial; LV, left ventricular; LVMI, left ventricular mass index; MI, myocardial infarction; PARTNER 2, Placement of Aortic Transcatheter Valve 2; RAS, renin-angiotensin system; SAVR, surgical aortic valve replacement; STS/ACC/TVT, Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapies; and TAVR, transcatheter aortic valve replacement.
non-RAS group (99%, 90%, and 71% versus 96%, 78%, and 49%, respectively; \(P<0.001\)). The survival benefit associated with RAS blockade was consistent across various prespecified subgroups stratified by concomitant coronary artery bypass grafting with SAVR, sex, age cutoff of 75 years, diabetes mellitus, LV dysfunction, hypertension, atrial fibrillation, and aortic valve gradient. For the matched cohorts, on echocardiographic analysis there were no significant group differences between the RAS and non-RAS groups with respect to change in left ventricular mass index (LVMI) \((P=0.37)\), LVEF \((P=0.67)\), and left atrial size \((P=0.43)\) after SAVR. The authors hypothesized that the increased survival rates associated with RAS blockade therapy may be related to several mechanisms:

1. **Cardioprotective effect.** RAS blockade has proven to be beneficial in patients with high risk for cardiovascular events, such as those with clinical evidence of atherosclerosis or diabetes mellitus, as in the HOPE (Heart Outcomes Prevention Evaluation) trial.\(^4\) The postulated mechanism of benefit associated with RAS blockade in the high-risk population undergoing AVR for severe AS include inhibition of vasoconstriction, atherosclerotic plaque stabilization and reduction in plaque rupture, and improved endothelial function.

2. **Regression of myocardial fibrosis.** This was not directly measured in this study since interstitial fibrosis cannot be quantified by echocardiography. Cardiac magnetic resonance imaging is a sensitive tool for quantifying myocardial fibrosis and may be an important part of future trial design for assessing myocardial changes following SAVR or TAVR.\(^5\)

3. **RAS blockade.** RAS blockade may be associated with reduction in arrhythmogenic death related to potassium-sparing effects.\(^4\) These mechanisms of benefit associated with RAS blockade after SAVR are speculative, and there are no trials to support or refute these hypotheses in this patient population.

There is only 1 published randomized study evaluating the effect of ARBs on LV remodeling after SAVR for severe AS.\(^3\) In that study, 114 patients were randomized in a 1:1 fashion to candesartan 32 mg daily (n=57) versus conventional treatment (n=57). The prespecified primary end point was change in LVMI, and secondary end points included change in left atrial volume index, N-terminal pro-B-type natriuretic peptide, and E′/E ratio. At 12 months, a significant decrease in LVMI was seen in the candesartan group compared with the control group (mean decrease in LVMI 30±40 g/m\(^2\) versus 12±28 g/m\(^2\); \(P=0.015\)). At 12 months, the LVMI was significantly lower in the candesartan group compared with control group (103±29 versus 119±31 g/m\(^2\); \(P=0.01\)). In addition, the candesartan group had greater improvement in longitudinal LV systolic function assessed by tissue Doppler S′ wave (0.6±0.1 cm/s increase in the control group versus 1.4±0.1 cm/s in the candesartan group; \(P=0.01\)) and a decrease in left atrial volume \((P=0.02)\).

The authors concluded that ARB therapy after AVR for severe AS is associated with augmented reverse LV and left atrial remodeling compared with conventional management. The authors point out that the mean decrease in LVMI of 30 g/m\(^2\) seen in this study is similar to mean 21 g/m\(^2\) decrease in LVMI in patients with hypertension treated with losartan in the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) study.\(^4\) Fewer patients treated with candesartan in this study developed atrial fibrillation, which suggests that the structural benefits seen in the candesartan arm may have clinical importance. The main limitations of this study were small sample size and lack of patient blinding to treatment allocation, introducing potential bias.

In a retrospective study of 508 consecutive patients undergoing isolated SAVR (ie, without concomitant coronary artery bypass grafting or other valve intervention), RAS blockade (n=286, 53%; ARB n=143, 28%; ACEI n=125, 25%) was associated with lower 30-day mortality in the ARB group compared with the no–RAS blockade group (0.7% versus 5.8%; \(P=0.012\)) or compared with the ACEI group (0.7% versus 5.6%; \(P=0.019\)).\(^4\) Patients in the RAS blockade group had significantly better 8-year survival compared with those without RAS blockade (83±3% versus 52±5%; \(P<0.0001\)) and confirmed in a propensity score–matched pairs analysis (82±4% versus 50±7%; \(P<0.0001\)). Long-term survival was significantly better in those treated with ARBs compared with ACEIs in this study, and by multivariable analysis; ARBs remained significantly associated with improved survival compared with ACEIs. Echocardiographic data were not available in this study. The operative mortality of the study cohort was 4.3% (n=22), with no significant difference between the RAS blockade and no–RAS blockade groups (3% versus 5.8%; \(P=0.13\)); however, interestingly, treatment with an ARB was associated with reduced risk of operative mortality compared with patients without RAS blockade (odds ratio, 0.098; 95% CI, 0.013–0.756; \(P=0.026\)) or those treated with an ACEI (odds ratio, 0.119; 95% CI, 0.014 to −0.979; \(P=0.048\)). This operative mortality benefit remained in favor of the preoperative ARB group even after adjusting for EuroScore II (odds ratio, 0.098; 95% CI, 0.013–0.757; \(P=0.026\)). These findings suggest that preoperative treatment with an ARB may provide some global cardiovascular protective effect.
The authors hypothesize that the benefit associated with ARBs over ACEIs may in part be related to the fact that ARBs act further downstream in the RAS cascade, thus being more effective for angiotensin II inhibition.

In a retrospective study of 150 consecutive patients undergoing concomitant aortic and mitral valve replacement or dual valve replacement, use of an ACEI or ARB (n=62) was associated with improved composite end point of cardiovascular mortality and heart failure hospitalization (P=0.01) compared with no ACEI/ARB (n=88) over a median follow-up duration of 50 months.41 Findings were similar, in favor of ACEI/ARB therapy when patients were stratified on the basis of presence of LV dilatation (LV end-systolic diameter >4 cm) and impaired LV systolic function (LVEF <50%). After multivariable Cox regression analysis adjusted for age, New York Heart Association class, cardiovascular risk factors, LV dilatation, LVEF, use of an ACEI/ARB was found to be an independent variable associated with fewer adverse events as defined by the primary outcome (HR, 0.23; 95% CI, 0.08–0.67; P<0.01).

ROLE OF ACEI/ARB AFTER TAVR

The first retrospective study evaluating the impact of RAS blockade on outcomes after TAVR included 560 patients undergoing TAVR from 9 centers in Japan.46

The methodology is similar to the study from the Cleveland Clinic.38 Patients were stratified by RAS blockade therapy with an ACEI or ARB based on at least 2 prescriptions dispensed 180 days apart after TAVR. At 6 months after TAVR; compared with the non–RAS blockade group (n=189), the RAS blockade group (n=371) had significantly greater LV mass regression (−9±24% versus −2±25%; P=0.024). Overall mortality at 2 years was significantly lower in the RAS blockade group compared with the non–RAS blockade group (7.5% versus 12.5%; P=0.031). After adjusting for confounding factors, RAS blockade was associated with significantly lower all-cause mortality (HR, 0.45; 95% CI, 0.22–0.91; P=0.025). There was no significant difference in the rate of repeat hospitalization for heart failure between the 2 groups (5.9% versus 9.0%; P=0.18) (Table 2).

A multicenter study from Spain evaluated the impact of RAS blockade following TAVR in 2785 patients, of which 1622 (58%) patients were treated with RAS blockade therapy after TAVR.47 At median follow-up of 3 years after TAVR, the RAS blockade group had significantly lower cardiovascular mortality compared with the non–RAS blockade group (5.6% versus 9.5%; P<0.001). In addition, the rate of cerebrovascular events and readmissions was higher among patients not treated with RAS inhibition. In a multivariate analysis, the use of RAS inhibitors at discharge following successful TAVR was the only independent protective factor against cardiovascular death (HR, 0.59; 95% CI, 0.41–0.87; P=0.007). Patients treated with RAS inhibition demonstrated larger decrease in end-diastolic and end-systolic volumes and larger regression of septal hypertrophy compared with patients without RAS inhibitors.

Recently, Inohara et al48 published a retrospective cohort study of TAVR procedures performed in the United States using the STS/ACC/TVT (Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapies) Registry to study the association of prescription of an RAS inhibitor and outcomes after TAVR. All consecutive patients >65 years of age with Medicare who underwent TAVR between July 2014 and January 2016 were included. The exposure was prescription of an RAS inhibitor at hospital discharge. The primary outcomes studied were all-cause mortality and readmission attributable to heart failure at 1 year after hospital discharge, evaluated individually and using the Medicare Denominator File and in-hospital administrative claims data. Secondary outcomes evaluated include health status assessed by Kansas City Cardiomyopathy Questionnaire at 1 year. Among 21 312 patients who underwent TAVR at 417 US sites, 8468 patients (39.7%) were prescribed a RAS inhibitor at hospital discharge. After propensity matching, 15 896 patients with similar propensity scores for prescription of a RAS inhibitor were identified. Patients prescribed a RAS inhibitor had significantly lower mortality rates at 1 year compared with patients with no prescription (12.5% versus 14.9%, respectively; absolute risk difference, −2.4% [95% CI, −3.5% to −1.4%]; HR, 0.82 [95% CI, 0.76–0.90]) and lower heart failure readmission rates at 1 year (12% versus 13.8%, absolute risk difference, −1.8% [95% CI, −2.8% to −0.7%]; HR, 0.86 [95% CI, 0.79–0.95]). When stratified by LVEF, patients prescribed a RAS inhibitor had lower 1 year mortality compared with patients without a prescription (11.1% versus 13.9%; HR, 0.78; 95% CI, 0.71–0.86) only in those with preserved LVEF and not in those with reduced LVEF (18.8% versus 19.5%; HR, 0.95; 95% CI, 0.81–1.12). Of 15 896 matched patients, 4837 (30.4%) were included in the Kansas City Cardiomyopathy Questionnaire score analysis and improvements at 1 year were greater in patients prescribed a RAS inhibitor post TAVR compared with those without a prescription (median adjusted change in Kansas City Cardiomyopathy Questionnaire score, 33.3 [interquartile range, 14.2–51.0] versus 31.3 [ interquartile range, 13.5–51.1]; difference in improvement, 2.10; [95% CI, 0.10–4.06]; P=0.001), however, the effect size was less than the minimal clinically
important difference of 5 points. Despite the inherent limitations of such a retrospective analysis, mainly related to unmeasured or residual confounding, this is the largest study to date, demonstrating a lower risk of mortality and heart failure readmission associated with prescription of a RAS inhibitor at hospital discharge after TAVR compared with those without a prescription.

Data were analyzed from the PARTNER trial and registries including 3979 intermediate, high, and prohibitive surgical risk patients who underwent TAVR to study the association between treatment with ACEI/ARB at baseline and clinical outcomes. Patients were stratified on the basis of ACEI/ARB use at baseline and 1736 (43.6%) were treated and 2243 (56.4%) were not treated with an ACEI/ARB at baseline. The primary end point was all-cause mortality. Treatment with an ACEI/ARB was associated with lower 2-year all-cause mortality (18.6% versus 27.5%; \(P<0.0001\)), cardiovascular mortality (12.3% versus 17.9%; \(P<0.0001\)) and noncardiovascular mortality (7.2% versus 11.7%; \(P<0.0001\)). Treatment with an ACEI/ARB at baseline remained independently associated with a lower hazard of 2-year all-cause and cardiovascular mortality after multivariable adjustment and propensity score matching.

Based on significant beneficial effects of RAS blockade therapy in patients with AS summarized above, a multicenter, open-label, randomized 1:1 trial—the RASTAVI (RAS Blockade After TAVI) study is under way. This trial aims to investigate the effect of adding ramipril to standard care in patients successfully treated with TAVI. Primary outcomes to be studied include reduction in cardiac mortality, heart failure admissions, and cerebrovascular events at 3-year follow-up. Secondary outcomes include LV remodeling determined by ventricular mass, fibrosis, LVEF as assessed by cardiac magnetic resonance imaging, and functional capacity after 1 year. This will be an important study that will provide randomized data on impact of RAS blockade after TAVR and the results, if positive in favor of RAS blockade, will help improve outcomes of patients undergoing TAVR. Randomized trials of RAS inhibition in patients with AS are warranted on the basis of available literature summarized above.

RAS BLOCKADE AND RISK OF CORONAVIRUS DISEASE 2019

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2. The virus infects cells by way of interaction with ACE2, a functional receptor expressed in the lungs and other tissues in addition to the cardiovascular system. Patients with underlying cardiovascular diseases appear to have an increased risk for adverse outcomes with COVID-19. A large number of patients with cardiovascular disease such as heart failure and hypertension are on RAS inhibitors such as ACEIs or ARBs. These drugs can increase tissue expression of ACE2 and its presentation at the cell surface. Concerns have been raised regarding upregulation of ACE2 with the use of RAS inhibitors, and consequent increase in risk of COVID-19 after exposure to severe acute respiratory syndrome coronavirus 2. On the contrary, there are also speculations that use of RAS inhibitors may be beneficial to patients with COVID-19 given that unopposed angiotensin II activity is believed to be involved in the disease pathogenesis. Currently, there are no experimental or clinical data demonstrating beneficial or adverse outcomes with baseline use of RAS inhibitors in COVID-19 or among patients with COVID-19 with history of cardiovascular disease treated with these agents. In an observational analysis in a cohort of more than 12,500 patients tested for COVID-19 in a large health system in New York City, previous treatment with RAS inhibitors was not associated with higher risk of testing positive for COVID-19 or the likelihood of severe COVID-19 among patients with a positive test. The Heart Failure Society of America, American College of Cardiology and the American Heart Association recommend continuation of RAS inhibitors for patients who are presently taking these for proven indications such as heart failure, hypertension, or ischemic heart disease.

ARTICLE INFORMATION

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Disclosures
Dr Goel is on the Speakers Bureau for Abbott Structural Heart. Dr Reardon is a consultant for Medtronic. The remaining authors have no disclosures to report.

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