Management of Hypertension in Patients With Mild to Moderate Aortic Stenosis

Navigating the SEAS

The treatment of hypertension has been the subject of intense interest and debate over the last several years.1–5 Although a “lower is better strategy” has been adopted in clinical practice for many but not all patient cohorts, the boundary conditions for blood pressure treatment have not been established rigorously by clinical trials involving middle-aged and older adults with hypertension and other prespecified cardiovascular disorders such as acute coronary syndromes, heart failure, and valvular heart disease. Concern remains that a J- or U-curve association between blood pressure and outcomes exists in vulnerable patients with impaired coronary flow reserve or myocardial dysfunction.6 Excessive lowering of the diastolic blood pressure (DBP) may result in critical reductions in coronary perfusion pressure below the autoregulatory limit and render the heart ischemic, especially when myocardial oxygen demand is increased. Nevertheless, the evidence base is not uniformly consistent, and issues such as confounding and reverse causality have been invoked to explain the observations made in some but not all trials.5 The deleterious effects of significantly elevated systolic blood pressure (SBP) or DBP, however, across essentially all patient populations are not in question.

The prevalence of hypertension and significant valvular heart disease, especially calcific aortic valve stenosis, increases with age,7,8 and their combined treatment can prove quite challenging. Older patients not uncommonly have coexistent coronary or cerebrovascular disease, chronic kidney disease, atrial fibrillation, and diabetes mellitus, comorbidities that further complicate management decisions and argue for an individualized approach. Polypharmacy, drug-drug interactions, side effects, and cost are additional considerations. For the practitioner trying to strike the right balance, it would be useful to know the range of blood pressures within which treatment might be considered effective and safe.

The primary results of the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) were published in 2008.9 Investigators from Scandinavia, Germany, the United Kingdom, and Ireland randomized 1873 patients (mean age, 67 years; range, 45–85 years) with mild to moderate aortic stenosis (AS), normal left ventricular (LV) systolic function, and no traditional indication for lipid-lowering therapy to simvastatin 40 mg plus ezetimibe 10 mg or placebo and demonstrated no significant between-group differences in a composite end point of major cardiovascular events or in the rate of progression or course of AS over a median follow-up of 52 months despite a 54% reduction in low-density lipoprotein cholesterol levels in the active treatment arm. Although historically viewed as a “negative” trial, the SEAS study has proven to be a robust source of information on the natural history and assessment of AS. In SEAS, ≈50% of patients had a history of hypertension or elevated blood pressure at baseline, and comparable numbers of patients in both groups were taking angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (25%), calcium channel blockers (17%), and/or β-blockers (28%). The effects of hypertension on LV struc-

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ture and outcomes were reported in 2012.\textsuperscript{10} Mean blood pressures at entry were 152/84 and 125/76 mmHg, respectively, for hypertensive and normotensive patients. SBP at the final study visit averaged 140 to 145 mmHg among those who were hypertensive at baseline. The prevalence of LV hypertrophy increased 3-fold in both the hypertensive and nonhypertensive patient groups. Hypertension predicted a 50\% higher incidence of abnormal LV geometry (hypertrophy, remodeling) at the final study visit and was associated with a 56\% higher rate of ischemic cardiovascular events and a 2-fold increased rate of death independently of AS severity, study treatment, in-treatment SBP, and abnormal LV geometry. Hypertension was not associated with an increased rate of the need for aortic valve replacement. The investigators postulated that the adverse effects of hypertension in this population were mediated by its influence on the progression of coronary atherosclerosis.

In this issue of Circulation, the SEAS Investigators extend their prior observations on the association between hypertension and midterm outcomes (4.3 years) in an attempt to determine whether recommendations can be made on optimal blood pressure targets for patients with these 2 common disorders.\textsuperscript{13} Admittedly, the study is limited by virtue of its post hoc, observational nature and the reliance on a cumulative average blood pressure derived from relatively few isolated determinations over the course of the trial. Lowest event rates were seen in the blood pressure range of 120 to 139/70 to 79 mmHg. All-cause mortality was significantly associated with average SBP <120 mmHg and DBP ≥90 mmHg, respectively. Elevated average DBP (≥90 mmHg) was consistently associated with every outcome assessed except the need for aortic valve replacement in patients with mild AS at baseline, whereas low average DBP (<70 mmHg) was associated with all-cause mortality and heart failure, but only in patients with moderate AS at baseline. A J- or U-curve association was demonstrated for cumulative average SBP and DBP and all-cause mortality (Figure 1, left). Nonlinear relationships between time-varying SBP and all-cause death, cardiovascular mortality, need for aortic valve replacement, and heart failure were also shown. In a spline analysis using time-varying SBP of 130 to 139 mmHg as reference, mortality risk was increased with SBP >160 mmHg and SBP <130 mmHg after adjustment for DBP and age. Incorporating the results of the numerous tests for association conducted, the authors suggest that a target blood pressure of 130 to 139/70 to 90 mmHg should be considered for patients with mild to moderate AS and hypertension.

The nonlinear relationships (J or U curve) between outcomes and DBP reported by the SEAS Investigators parallel those observed in patients with acute coronary syndromes\textsuperscript{12} and in patients with coronary artery disease, hypertension, and diabetes mellitus.\textsuperscript{13} They are consistent with the notion that critical reductions in coronary perfusion pressure can have deleterious consequences in vulnerable patients with preexisting large- or small-vessel coronary artery disease, abnormal coronary flow reserve, and altered myocardial properties. As is true for virtually every cardiovascular condition, DBP in excess of 90 mmHg equates with poor outcomes and should be avoided. The survival hazard for time-varying SBP <130 mmHg is not readily explained, nor is its association with an increased need for aortic valve replacement over follow-up. Perhaps low SBP is a marker of another, unmeasured variable that affects prognosis in patients with less than severe AS. It seems unlikely that patients in this trial were exposed to excessive hypotension from intensive blood pressure-lowering treatments. SBPs in excess of 160 mmHg would significantly increase the resistance load on the LV and hasten the development of hypertrophy and adverse remodeling. Hypertension has also been implicated as a risk factor for aortic valve inflammation, fibrosis, and calcification.\textsuperscript{14}

Clinical practice guidelines recommend that hypertension be treated in patients with AS.\textsuperscript{15,16} They also remind us that hypertension can interfere with the accurate assessment of AS severity and that valve and LV hemodynamics should be re-evaluated after optimal blood pressure control. This latter caveat is especially true for patients with low-flow, low-gradient AS and normal ejection fraction. The SEAS Investigators have previously enlightened us about the adverse impact of hypertension on the natural history of mild to moderate AS with normal LV systolic function (stage B disease) and now provide the clinician with reasonable blood pressure boundaries within which to manage this challenging group of patients. A cautious, progressive, individualized, pharmacological approach after lifestyle changes have been implemented is always advised, but no class of medications should be considered strictly out of bounds.

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FOOTNOTES

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REFERENCES

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