Hypertension in Aortic Stenosis
Implications for Left Ventricular Structure and Cardiovascular Events

Åshild E. Rieck, Dana Cramariuc, Kurt Boman, Christa Gohlke-Bärwolf, Eva M. Staal, Mai Tone Lønnebakken, Anne B. Rossebø, Eva Gerdts

Abstract—The impact of hypertension on left ventricular structure and outcome during progression of aortic valve stenosis has not been reported from a large prospective study. Data from 1616 patients with asymptomatic aortic stenosis randomized to placebo-controlled treatment with combined simvastatin and ezetimibe in the Simvastatin Ezetimibe in Aortic Stenosis Study were used. The primary study end point included combined cardiovascular death, aortic valve events, and ischemic cardiovascular events. Hypertension was defined as history of hypertension or elevated baseline blood pressure. Left ventricular hypertrophy was defined as left ventricular mass/height$^{2.7}$ $\geq$ 46.7 g/m$^{2.7}$ in women and $\geq$ 49.2 g/m$^{2.7}$ in men and concentric geometry as relative wall thickness $\geq$ 0.43. Baseline peak aortic jet velocity and aortic stenosis progression rate did not differ between hypertensive (n = 1340) and normotensive (n = 276) patients. During 4.3 years of follow-up, the prevalence of concentric left ventricular hypertrophy increased 3 times in both groups. Hypertension predicted 51% higher incidence of abnormal LV geometry at final study visit independent of other confounders ($P$<0.01). In time-varying Cox regression, hypertensive did not predict increased rate of the primary study end point. However, hypertension was associated with a 56% higher rate of ischemic cardiovascular events and a 2-fold increased mortality (both $P$<0.01), independent of aortic stenosis severity, abnormal left ventricular geometry, in-treatment systolic blood pressure, and randomized study treatment. No impact on aortic valve replacement was found. In conclusion, among patients with initial asymptomatic mild-to-moderate aortic stenosis, hypertension was associated with more abnormal left ventricular structure and increased cardiovascular morbidity and mortality. (Hypertension. 2012;60:00-00.)

Key Words: hypertension ■ aortic valve stenosis ■ echocardiography ■ prognosis ■ antihypertensive agents

Among older patients with aortic stenosis (AS), hypertension (HT) is a common comorbidity found in up to 78% of patients.1–4 HT is a known predictor of increased cardiovascular (CV) morbidity and mortality both in general and HT populations,5,6 but it is unknown whether concomitant HT is associated with increased CV event rate in AS.

In patients with asymptomatic mild-to-moderate AS, concomitant HT has been associated with higher prevalence of left ventricular (LV) hypertrophy, particularly of eccentric type.1 In contrast, a retrospective study in patients with severe symptomatic AS reported comparable prevalence of LV hypertrophy in HT and normotensive patients with a preponderance of concentric LV geometry irrespective of the presence of HT.5 However, the impact of concomitant HT on changes in LV structure during progression of AS has not been reported previously from a large, prospective study. The aim of the present study was to assess these questions within the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) Study, including initially asymptomatic patients with mild-moderate AS without diabetes mellitus or prevalent CV disease.

Patient Population
The present analysis was prospectively planned within the SEAS Study, approved by the Scientific Steering Committee in 2002. The SEAS Study randomized 1873 patients aged 45 to 85 years with asymptomatic AS to a fixed combination of simvastatin 40 mg and ezetimibe 10 mg once daily to evaluate the effect on progression of AS and CV events. Study organization, design, patient recruitment, and main outcome of SEAS has been published previously.7,8 Of note, patients with other significant valvular disease, rheumatic valvular disease, prosthetic heart valves, diabetes mellitus, or known atherosclerotic disease were not included in the SEAS Study. All of the patients gave written informed consent, and ethical committees in all of the participating countries approved the study. HT was defined as history of HT or use of antihypertensive treatment reported by the attending physician or elevated blood pressure at the baseline clinical visit (systolic blood pressure $\geq$ 140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg).9 Blood tests were analyzed at the SEAS core laboratory, PPD Global Central Laboratories (Zaventem, Belgium).

The present study population includes the 1616 patients in whom LV structure could be assessed on the baseline and $\geq$ 1 follow-up study echocardiogram before the occurrence of any CV study end point. Compared with the present study population, the 257 excluded patients

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From the Institute of Medicine (A.E.R., M.T.L., E.G.), University of Bergen, Bergen, Norway; Department of Heart Disease (D.C., M.T.L., E.G.), Haukeland University Hospital, Bergen, Norway; Department of Medicine (K.B.), Skelleftea Hospital and Umea University, Skelleftea, Sweden; Herz-Zentrum Bad Krozingen (C.G.-B.), Bad Krozingen, Germany; Department of Cardiology (E.M.S.), Stavanger University Hospital, Stavanger, Norway; Division of Cardiology (A.B.R.), Aker University Hospital, Oslo, Norway.
Correspondence to Åshild E. Rieck, Institute of Medicine, University of Bergen, 5021 Bergen, Norway. E-mail ashild.rieck@gmail.com

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Table 1. Baseline Characteristics in Normotensive and Hypertensive Groups of Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normotensive Patients (n=276)</th>
<th>Hypertensive Patients (n=1340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±11</td>
<td>68±9*</td>
</tr>
<tr>
<td>Body mass index, g/m²</td>
<td>25.5±3</td>
<td>27.1±4*</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.90±0.2</td>
<td>1.89±0.2</td>
</tr>
<tr>
<td>Women, %</td>
<td>27</td>
<td>42*</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>125±9</td>
<td>152±20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76±7</td>
<td>84±10</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>92±6</td>
<td>107±11</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>50±10</td>
<td>68±18</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>0</td>
<td>61</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64±10</td>
<td>66±12†</td>
</tr>
<tr>
<td>Antihypertensive drug treatment, %</td>
<td>0</td>
<td>68</td>
</tr>
<tr>
<td>No. of antihypertensive drugs, n</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors, %</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Angiotensin receptor blockers, %</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Calcium antagonists, %</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>β-blockers, %</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>α-blockers, %</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.7±1.0</td>
<td>5.7±1.0</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.6±0.9</td>
<td>3.6±0.9</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.5±0.4</td>
<td>1.5±0.4</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.4±0.7</td>
<td>1.4±0.7</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min per 1.73 m²</td>
<td>88±16</td>
<td>85±17†</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

*P<0.01 vs normotensive patients.
†P<0.01 vs normotensive patients.
‡P<0.05 vs normotensive patients.

did not differ in prevalence of HT, age, blood pressure, or sex distribution.

Echocardiography

Study echocardiograms were obtained at 173 study centers in Denmark, Finland, Germany, Ireland, Norway, Sweden, and the United Kingdom following a standardized protocol and sent for blinded expert interpretation at the SEAS echocardiography core laboratory at Haukeland University Hospital. The echocardiographic methods have been published previously.10,11 All of the reading was performed using offline digital workstations with Image Arena (TomTec Imaging Systems GmbH, Unterschleisheim, Germany) software. Severity of AS, LV structure, and systolic function were measured following the joined European Association of Echocardiography and American Society of Echocardiography guidelines.12,13 Teichholz-derived LV volumes were used for the calculation of stroke volume and cardiac output.14 Circumferential end-systolic stress was estimated at midwall, and actual and predicted midwall shortening were calculated using standard equations.12,15 LV hypertrophy was considered present when LV mass/height2.7 exceeded 46.7 g/m² in females and 49.2 g/m² in men, respectively.5,16 Relative wall thickness was calculated as LV posterior wall thickness/LV internal radius at end diastole and considered increased if ≥0.43.17 LV geometry was assessed from LV mass/height2.7 and relative wall thickness in combination grouping patients with normal LV mass/height2.7 into normal geometry or concentric remodeling patterns and patients with elevated LV mass/height2.7 into eccentric and concentric LV hypertrophy patterns, respectively.

Study End Points

All of the end points were adjudicated by an independent committee blinded to study treatment. The prespecified primary end point of the study was major CV events, a composite end point including death from CV causes, aortic valve–related events, and ischemic CV events.7 The secondary end points were aortic valve events (combined congestive heart failure attributed to progression of AS, aortic valve replacement, and death from CV causes) and ischemic CV events (combined death from CV causes, nonfatal myocardial infarction, hospitalization for unstable angina, coronary revascularization, and nonhemorrhagic stroke) analyzed separately. Total mortality was a prespecified tertiary end point.

Statistics

SPSS 18.0 (SPSS Inc, Chicago, IL) software was used for data management and analysis. Data are expressed as mean±SD for continuous variables and as percentages for categorical variables. Comparisons between groups were done using the Student t test for baseline characteristics, ANOVA for repeated measures, and χ² tests as appropriate.

The last study echocardiogram was defined as the last performed before a CV event in patients who experienced end points during follow-up and as the final study echocardiogram in patients without

Figure 1. Change in systolic blood pressure in hypertensive (solid line) and normotensive (dotted line) groups of patients during follow-up.

Aortic valve area corrected for pressure recovery in the aortic root (energy loss index) was calculated using previously published equations.18 Aortic regurgitation was assessed by color Doppler using a previously described 4-point grading system.19 Valvuloarterial impedance, a measure of the combined valvular and arterial load in AS, was calculated by the method of Briand et al20 using Teichholz-derived stroke volume indexed to height in the allometric power of 2.04.21 Stroke work loss was calculated as Doppler-derived mean aortic valve gradient over the sum of systolic blood pressure and mean transaortic gradient.22,23 Systemic arterial compliance was calculated as stroke volume indexed for body surface area/pulse pressure ratio and total peripheral resistance as (80×mean blood pressure/cardiac output), using brachial blood pressure. Blood pressure measured at the end of the echocardiography with the patients still in the supine position was used for the calculation of hemodynamic variables.

Hypertensive Groups of Patients

July 2012
CV events. To assess the impact of HT on new-onset abnormal LV geometry, multivariate logistic regression analysis was used.

Univariate and time-varying multivariate Cox regression analyses were performed to assess the impact of HT on outcome. The primary multivariate model included systemic arterial compliance, mean aortic jet velocity, and abnormal LV geometry as time-varying covariates and randomized study treatment as a fixed covariate. In further models, antihypertensive drug treatment and type of antihypertensive drug were included. A 2-tailed \( P \leq 0.05 \) was considered statistically significant both in univariate and multivariate analyses.

Results

Patient Characteristics

Compared with normotensive patients, HT patients were older and included more women (Table 1). A total of 68.5% of HT patients used antihypertensive treatment, on average, 1.1 drugs (Table 1). Systolic blood pressure decreased during the first study years in the HT group. In contrast, a small increase in systolic blood pressure was found in the normotensive group during the first year (Figure 1). Similar changes were found for diastolic blood pressure (data not shown). AS severity did not differ between groups when measured as peak aortic jet velocity, mean transvalvular gradient, or unadjusted aortic valve area at baseline, but HT patients had lower energy loss index (Table 2). The prevalence of aortic regurgitation was similar in both groups, and the regurgitation was predominantly of a mild degree (grade 1 in >70% in both groups). Valvuloarterial impedance and stroke work loss were higher in HT patients, and HT patients also had lower systemic arterial compliance and higher peripheral arterial resistance and LV end-systolic stress (all \( P \leq 0.01 \); Table 2). AS progression rate did not differ between HT and normotensive groups; annual decrease in aortic valve area was 0.03 ± 0.01 cm\(^2\)/year versus 0.04 ± 0.02 cm\(^2\)/year and annual increase in peak aortic jet velocity increased with 0.19 ± 0.01 m/s/year versus 0.22 ± 0.03 m/s/year, whereas annual increase in mean aortic gradient was 4 mm Hg per year in both groups (all \( P > 0.17 \)).

Change in LV Geometry During Follow-Up

HT patients had larger LV mass/height\(^{0.7} \) throughout the course of the study (Figure 2 and Table 2). Eccentric LV hypertrophy was the most common type of abnormal LV geometry at baseline. During follow-up, the prevalence of concentric LV hypertrophy increased 3 times and became the most common abnormal LV geometry in both groups (Figure 3). However, abnormal LV geometry remained more prevalent in the HT group throughout the study (Figure 3). Among patients with normal LV geometry at baseline (n=903), HT predicted a 51% higher risk of having abnormal LV geometry on the last study echocardiogram (hazard ratio, 1.51 [95% CI, 1.03–2.21]; \( P = 0.04 \)) even after adjustment for severity of AS, age, ejection fraction, sex, and systolic blood pressure at the last study visit. Of note, 49% of HT patients with eccentric LV hypertrophy at baseline had concentric LV hypertrophy at final study visit. In the subset of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normotensive Patients (n=276)</th>
<th>Hypertensive Patients (n=1340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak aortic jet velocity, m/s</td>
<td>3.0 ± 0.5</td>
<td>3.0 ± 0.5</td>
</tr>
<tr>
<td>Aortic valve area, cm</td>
<td>1.33 ± 0.5</td>
<td>1.29 ± 0.5</td>
</tr>
<tr>
<td>Mean aortic valve gradient, mm Hg</td>
<td>22 ± 8</td>
<td>22 ± 8</td>
</tr>
<tr>
<td>Energy loss index, cm/m^2</td>
<td>0.97 ± 0.51</td>
<td>0.92 ± 0.43</td>
</tr>
<tr>
<td>Valvuloarterial impedance, mm Hg/mL · m^2.04</td>
<td>5.9 ± 1.6</td>
<td>6.6 ± 2.1</td>
</tr>
<tr>
<td>Aortic annulus diameter, cm</td>
<td>2.26 ± 0.3</td>
<td>2.18 ± 0.3</td>
</tr>
<tr>
<td>Stroke work loss, %‡</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Left ventricular diameter at end diastole, cm</td>
<td>5.1 ± 0.7</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td>Left ventricular diameter at end systole, cm</td>
<td>3.2 ± 0.6</td>
<td>3.2 ± 0.5</td>
</tr>
<tr>
<td>Interventricular septum thickness at end diastole, cm‡</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Left ventricular posterior wall thickness at end diastole, cm‡</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Relative wall thickness‡</td>
<td>0.35 ± 0.08</td>
<td>0.36 ± 0.09</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>66 ± 7</td>
<td>66 ± 6</td>
</tr>
<tr>
<td>Circumferential end-systolic stress, kdyne/cm^2‡</td>
<td>102 ± 29</td>
<td>114 ± 32</td>
</tr>
<tr>
<td>Stress-corrected midwall shortening, %*</td>
<td>99 ± 19</td>
<td>98 ± 20</td>
</tr>
<tr>
<td>Left ventricular mass, g*</td>
<td>178 ± 61</td>
<td>194 ± 67</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, %</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Systemic arterial compliance, mL/m^2 per mm Hg‡</td>
<td>0.87 ± 0.36</td>
<td>0.67 ± 0.24</td>
</tr>
<tr>
<td>Total peripheral resistance, dyne · s · cm^-5‡</td>
<td>1644 ± 472</td>
<td>1779 ± 611</td>
</tr>
<tr>
<td>Aortic regurgitation, %</td>
<td>58</td>
<td>60</td>
</tr>
</tbody>
</table>

Data from baseline, y 1, y 2, and final visit are included in analysis. Only data from first and last visit are shown.

*\( P < 0.05 \) vs normotensive patients using ANOVA for repeated measures.

†\( P < 0.01 \) vs normotensive patients using ANOVA for repeated measures.

‡\( P < 0.001 \) vs normotensive patients using ANOVA for repeated measures.
undergoing aortic valve replacement (n=401), there were no significant differences in LV geometry between the normotensive and HT patients either at baseline or at the last visit before surgery.

Impact of HT on CV Events

Incidences of the primary study end point and of the secondary end point aortic valve events did not differ between normotensive patients (35% and 33%) and HT patients (34% and 32%, both \( P>0.75 \)) during follow-up. In contrast, the rate of the secondary end point ischemic CV events was significantly higher in the HT group (17.3% versus 10.5% in the normotensive group; \( P<0.01 \)). In particular, HT was associated with higher incidence of angiographic coronary artery disease needing additional coronary artery bypass grafting during planned aortic valve replacement (9.6% versus 5.1% in the normotensive group, \( P<0.05 \)), whereas no significant association with stroke or myocardial infarction was found. Both CV and total mortality were higher among HT patients (4.9% versus 2.2% and 9.7% versus 4.7%, respectively, both \( P<0.05 \); Figure 4). Percutaneous coronary intervention was 3.5-fold more common in the HT group (1.4% in HT versus 0.4% in the normotensive group), but the difference was not statistically significant, probably because of the low incidence of this event (20 percutaneous coronary interventions) in our study population. In a multivariate Cox regression model, HT predicted a higher rate of combined ischemic CV events independent of randomized study treatment and time-varying systolic blood pressure, peak aortic jet velocity, and abnormal LV geometry (Table 3). When analyzing the individual composites of ischemic CV event end points, HT particularly predicted a 2-fold higher need for coronary artery bypass grafting at the time of planned aortic valve replacement, as well as a 2-fold higher risk of CV death in univariate analyses (Table 3).

Replacing HT with antihypertensive treatment in the model demonstrated that use of antihypertensive treatment predicted higher risk for ischemic CV independent of significant associations of systolic blood pressure (Table 4). Replacing antihypertensive treatment with type of antihypertensive drugs as individual variables revealed that treatment with \( \beta \)-blockers predicted higher risk of ischemic CV events (hazard ratio, 2.04 [95% CI, 1.08–3.85]; \( P=0.03 \)), whereas other antihypertensive drug classes were not independently associated with outcome.
Discussion

HT is a common comorbidity in patients with AS and is known to influence both assessment of AS severity and LV structure.\textsuperscript{2,3,24,25} This is the first large prospective analysis to assess the impact of HT on change in LV geometry and on patient outcome in initial asymptomatic AS. The study adds to previous knowledge by demonstrating that, during progression of AS, HT was associated with progressively more abnormal LV geometry, as well as a higher risk of death and of ischemic CV events.

Abnormal LV geometry is known to predict CV events in HT, as well as in normotensive populations.\textsuperscript{6,26,27} We have demonstrated previously that HT is the main determinant of abnormal LV geometry in asymptomatic mild-to-moderate AS and is particularly associated with eccentric LV hypertrophy, reflecting findings in patients with essential HT.\textsuperscript{1,24} Based on the postulate by Grossman et al.,\textsuperscript{28} concentric LV hypertrophy is the expected adaptation to AS, whereas HT may lead to different types of LV geometric adaptation, depending on the dominant clinical and hemodynamic factors.\textsuperscript{1,24} As proof of concept, a retrospective study by Antonini-Canterin et al.,\textsuperscript{4} including 193 patients with severe, symptomatic AS, found that concentric LV hypertrophy was the most prevalent abnormal LV geometry both in normoten-sive and HT patients. The present large prospective study in initially mild-to-moderate asymptomatic AS adds to this knowledge by demonstrating that progression of AS is associated with a change from predominantly normal geometry, with eccentric hypertrophy being the most frequent abnormal LV geometric pattern, to predominantly concentric LV geometry both in normotensive and HT patients. However, in spite of a 3-fold increase in the prevalence of concentric LV hypertrophy both in normotensive and HT patients during follow-up, concomitant HT was independently associated with more abnormal LV geometry throughout the study, probably reflecting the higher global valvuloarterial load in the HT group.

The ≈2-fold increased risk of death and of ischemic CV events associated with HT in the present study population, independent of important prognosticators like AS severity and abnormal LV geometry, is in line with findings in a meta-analysis of 61 prospective studies investigating the relationship between HT and ischemic CV mortality.\textsuperscript{29} In Figure 4, Kaplan-Meyer plots of time to aortic valve events (A), ischemic cardiovascular (CV) events (B), CV death (C), and death from any cause (D) in normotensive (dotted line) and hypertensive (solid line) patient groups.
O'Brien et al35 showed that angiotensin-converting enzyme inhibitors, a prospective study of antihypertensive treatment safety and effects in AS patients treated with renin-angiotensin blockers nor prevalence of HT was provided in the publication.37 However, LV systolic function was normal in the majority of patients and history of diabetes mellitus or previous CV disease found in less than one third of patients, making it likely that HT was the predominant indication for renin-angiotensin blockers in their study population. The present study did not confirm these results. In contrast, antihypertensive treatment predicted an increased risk of ischemic CV events in the present study, independent of systolic blood pressure, AS severity, and abnormal LV geometry, possibly reflecting that AS patients treated for HT had more severe subclinical CV disease than is captured by standard echocardiography and clinical blood pressure measurement.39 The findings that α-blockers were the only type of antihypertensive medication associated with significantly increased CV events is in accordance with previous results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.39

Of note, the SEAS Study was not a dedicated study on HT in AS. HT was defined as a composite of either history of HT or use of antihypertensive therapy reported by the study center physician or presence of elevated blood pressure at the baseline clinic visit (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg). We cannot exclude that our definition of HT may have erroneously classified some normotensive patients as being HT based on a single visit blood pressure measurement. However, such an inclusion of normotensive patients in the HT group would diminish group differences, suggesting that the impact of HT on LV geometry and CV events may be even larger than those demonstrated in the present study.

**Perspectives**

HT is a common comorbidity in AS and is associated with more atherosclerosis, coronary artery disease, and increased mortality, as demonstrated by the present findings. Based on the different results from the present study demonstrating that HT treatment, in particular with α-blockers, is associated with increased risk for CV events in AS and the findings in the retrospective Scottish registry study in Tayside suggesting reduced mortality in AS patients treated with angiotensin-converting enzyme inhibitors, a prospective study of antihypertensive treatment safety and effects in AS is warranted.

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Novelty and Significance

What Is New?
- This is the first large prospective study to assess the influence of HT in patients with AS.
- Concomitant HT was independent of AS severity associated with more abnormal LV geometry.
- Concomitant HT was associated with a 2-fold higher mortality and a 56% increased rate of ischemic CV events.

What Is Relevant?
- HT is a common comorbidity in AS.
- Further studies are needed to test whether modern antihypertensive treatment modifies the prognostically unfavorable consequences of HT demonstrated in the SEAS Study.

Summary
In patients with AS participating in the SEAS Study, concomitant HT was associated with more abnormal LV geometry and higher CV morbidity and mortality.
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