New Insights Into the Progression of Aortic Stenosis
Implications for Secondary Prevention

Sanjeev Palta, MD; Anita M. Pai, MD; Kanwaljit S. Gill, MD; Ramdas G. Pai, MD

Background—The risk factors affecting aortic stenosis (AS) progression are not clearly defined. Insights into this may allow for its secondary prevention.

Methods and Results—We investigated predictors of AS progression in 170 consecutive patients with AS who had paired echocardiograms ≥3 months (23±11) apart. Various clinical, echocardiographic, and biochemical variables were related to the change in aortic valve area (AVA). The annual rate of reduction in AVA was 0.10±0.27 cm² or 7±18% per year. The reduction in AVA per year was significantly related to initial AVA (r=0.46, P<0.0001), the mean aortic valve gradient (r=0.27, P=0.04), left ventricular (LV) outflow tract velocity (r=0.26, P=0.001), and LV end-diastolic diameter (r=0.20, P=0.04) and marginally to serum creatinine level (r=0.15, P=0.08). Patients with a rate of reduction in AVA faster than the mean had higher serum creatinine (P=0.04) and calcium (P=0.08) levels. Those with a serum cholesterol level >200 mg/dL had a rate of AVA reduction roughly twice that of those with a lower cholesterol level (P=0.04). Stepwise multiple regression analysis identified initial AVA, current smoking, and serum calcium level as the independent predictors of amount of AVA reduction per year.

Conclusions—Absolute and percentage reduction in AVA per year in those with AS is greater in those with milder degrees of stenosis and is accelerated in the presence of smoking, hypercholesterolemia, and elevated serum creatinine and calcium levels. These findings may have important implications in gaining further insights into the mechanism of AS progression and in formulating strategies to retard this process. (Circulation. 2000;101:2497-2502.)

Key Words: valves ■ heart diseases ■ prevention ■ echocardiography

Aortic stenosis (AS) is common with the aging population. Symptomatic AS is associated with a poor prognosis, and this is improved by aortic valve replacement. Though the risk factors for the development of AS are the same as that of coronary artery disease,1 the factors affecting its progression are not clearly defined.2–6 Identification of risk factors for AS progression may allow for its secondary prevention. The present study was undertaken to investigate the rate of AS progression and to determine clinical, echocardiographic, and biochemical characteristics that may have a bearing on the progression of this disease process.

Methods

Patient Population
Subjects with any degree of AS seen in the echocardiographic laboratory and who had paired echocardiograms ≥3 (23±11) months apart were selected. Exclusion criteria included the presence of a congenital heart disease, bicuspid aortic valve, or previous valvular surgery. The study group consisted of 170 consecutive patients meeting these criteria.

Clinical and Biochemical Data
Clinical data including age, sex, history of current smoking, diabetes mellitus, hypertension, and end-stage kidney disease were obtained. Laboratory data included the serum calcium, phosphate, creatinine, uric acid, and cholesterol levels. These data were obtained from a combination of chart review and telephone interviews.

Echocardiographic and Doppler Data and Measurements
Echocardiographic examinations were performed with the use of standard techniques and commercially available equipment. Anatomic measurements were made according to the American Society of Echocardiography guidelines.7 The aortic valve area (AVA) was calculated by means of the continuity equation. The mean aortic valve gradient was obtained by tracing the continuous wave flow velocity signal across the aortic valve.

Statistics
Analysis was performed with the use of StatView version 4.5 (Abacus Concepts, Inc). Data are given as mean value±SD. Comparisons between groups were performed with the use of the χ² or unpaired t test. Linear regression analysis was used to investigate the relation between continuous variables. Stepwise multiple regression analysis was used to identify the independent predictors of AS progression. A value of P≤0.05 was taken to be significant, and a value between 0.05 and 0.10 was considered to be showing a trend toward significance.
The annual rate of reduction in AVA was 0.10 (range 0.07 to 0.27 cm² per year), indicating a wide variability in AS progression. As shown in Table 2, the absolute reduction in AVA per year was significantly related to initial AVA ($r=0.46$, $P<0.0001$), peak aortic valve velocity ($r=-0.28$, $P=0.0002$), the mean aortic valve gradient ($r=-0.27$, $P=0.016$), LV outflow tract velocity ($r=0.27$, $P=0.004$), and LV end-diastolic diameter ($r=0.20$, $P=0.04$) and marginally to the serum creatinine level ($r=0.15$, $P=0.08$). There was no significant correlation with age, ejection fraction, or serum cholesterol level.

### Correlates of Percentage Decrease in AVA per Year

The correlate of percentage decrease in AVA per year tends to correct the decrement in area to its initial area and the duration of follow-up (Table 2). The percentage reduction in AVA per year was significantly related to initial AVA ($r=0.30$, $P=0.0004$), peak aortic valve velocity ($r=-0.17$, $P=0.03$), the mean aortic valve gradient ($r=-0.28$, $P=0.04$), LV outflow tract velocity ($r=0.17$, $P=0.03$), and the serum calcium level ($r=0.21$, $P=0.008$) and marginally to serum calcium-phosphate product ($r=0.15$, $P=0.07$).

### Comparison of Rapid and Slow Progressors

At a percentage mean decrease in AVA per year of 7%, the patients were dichotomously divided into rapid (AVA reduction $\geq 7\%$ per year) and slow progressors (AVA reduction $<7\%$ per year). As shown in Table 3, the rapid progressors had larger initial AVA ($P=0.016$), smaller mean transvalvular gradient ($P=0.01$), and higher serum creatinine levels ($P=0.04$). In this group, there was a trend toward a higher preponderance of men ($P=0.10$), current

### Results

#### Baseline Patient Characteristics

Of the 170 subjects, 132 (78%) were men. Their age was 71±9 years. The initial AVA was 1.17±0.38 cm² (range 0.5 to 2.5). The left ventricular (LV) ejection fraction was 55±14% (range 15% to 85%). Concomitant aortic regurgitation was seen in 89 patients, being mild in 66, moderate in 18, and severe in 5. Mitral regurgitation was present in 78 patients: mild in 54, moderate in 17, and severe in 7 patients. One hundred patients had systemic hypertension, 38 were diabetics, 62 were smokers, 12 were on dialysis, and 60 had a serum cholesterol level $>200$ mg%. Table 1 further characterizes the study group.

#### Changes Over Time

The mean time interval between the 2 studies was 23±11 months, ranging from 3 to 66 months. Over this period of time, the mean AVA decreased from 1.17 to 1.01 cm² and mean systolic gradient increased from 20 to 27 mm Hg. The annual rate of reduction in AVA was 0.10±0.27 cm² or 7±18% per year when adjusted for the baseline AVA, indicating a wide variability in AS progression.

#### Correlates of Decrease in AVA per Year

As shown in Table 2, the absolute reduction in AVA per year was significantly related to initial AVA ($r=0.46$, $P<0.0001$), peak aortic valve velocity ($r=-0.28$, $P=0.0002$), the mean aortic valve gradient ($r=-0.27$, $P=0.016$), LV outflow tract velocity ($r=0.27$, $P=0.004$), and LV end-diastolic diameter ($r=0.20$, $P=0.04$) and marginally to the serum creatinine level ($r=0.15$, $P=0.08$). There was no significant correlation with age, ejection fraction, or serum cholesterol level.

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71±9</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>78</td>
</tr>
<tr>
<td>Current smoking</td>
<td>38%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>6%</td>
</tr>
<tr>
<td>LV outflow tract velocity, m/s</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>Peak aortic velocity, m/s</td>
<td>2.7±0.07</td>
</tr>
<tr>
<td>AVA, cm²</td>
<td>1.17±0.38</td>
</tr>
<tr>
<td>Mean systolic gradient, mm Hg</td>
<td>20±10</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>55±14</td>
</tr>
<tr>
<td>LV end-diastolic dimension, cm</td>
<td>5.1±0.9</td>
</tr>
<tr>
<td>LV end-systolic dimension, cm</td>
<td>3.4±1.1</td>
</tr>
<tr>
<td>Ventricular septum, cm</td>
<td>1.25±0.22</td>
</tr>
<tr>
<td>Posterior left ventricle wall, cm</td>
<td>1.19±0.18</td>
</tr>
<tr>
<td>Left atrial diameter, cm</td>
<td>4.3±0.8</td>
</tr>
<tr>
<td>Serum cholesterol level, mg/dL</td>
<td>186±52</td>
</tr>
<tr>
<td>Serum uric acid level, mg/dL</td>
<td>6.8±2.6</td>
</tr>
<tr>
<td>Serum creatinine level, mg/dL</td>
<td>1.6±1.4</td>
</tr>
<tr>
<td>Serum phosphate level, mg/dL</td>
<td>2.6±1.6</td>
</tr>
<tr>
<td>Serum calcium level, mg/dL</td>
<td>9.4±0.2</td>
</tr>
<tr>
<td>Serum calcium-phosphate product</td>
<td>24.2±16.2</td>
</tr>
</tbody>
</table>

### Table 2. Univariate Correlates of Absolute and Percent Reduction in AVA per Year

<table>
<thead>
<tr>
<th>Variable</th>
<th>Absolute AVA Reduction per Year</th>
<th>Percent AVA Reduction per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$r=0.02$ $P&gt;0.10$</td>
<td>$r=0.02$ $P&gt;0.10$</td>
</tr>
<tr>
<td>AVA</td>
<td>$r=0.46$ $P&lt;0.0001$</td>
<td>$r=0.3$ $P=0.0004$</td>
</tr>
<tr>
<td>LV outflow tract velocity</td>
<td>$r=0.26$ $P=0.001$</td>
<td>$r=0.17$ $P=0.03$</td>
</tr>
<tr>
<td>Peak aortic velocity</td>
<td>$r=-0.28$ $P=0.0002$</td>
<td>$r=-0.17$ $P=0.03$</td>
</tr>
<tr>
<td>Mean systolic gradient</td>
<td>$r=-0.27$ $P=0.04$</td>
<td>$r=-0.28$ $P=0.04$</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>$r=0.02$ $P&gt;0.10$</td>
<td>$r=0.02$ $P&gt;0.10$</td>
</tr>
<tr>
<td>LV end-diastolic dimension</td>
<td>$r=0.20$ $P=0.044$</td>
<td>$r=0.12$ $P&gt;0.10$</td>
</tr>
<tr>
<td>LV end-systolic dimension</td>
<td>$r=0.18$ $P=0.08$</td>
<td>$r=0.12$ $P&gt;0.10$</td>
</tr>
<tr>
<td>Ventricular septum</td>
<td>$r=-0.12$ $P&gt;0.10$</td>
<td>$r=-0.03$ $P&gt;0.10$</td>
</tr>
<tr>
<td>LV posterior wall</td>
<td>$r=0.01$ $P&gt;0.10$</td>
<td>$r=0.12$ $P&gt;0.10$</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>$r=0.09$ $P&gt;0.10$</td>
<td>$r=0.07$ $P&gt;0.10$</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>$r=0.064$ $P&gt;0.10$</td>
<td>$r=0.05$ $P&gt;0.10$</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>$r=0.013$ $P&gt;0.10$</td>
<td>$r=0.02$ $P&gt;0.10$</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>$r=0.15$ $P=0.08$</td>
<td>$r=0.12$ $P=0.16$</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>$r=0.04$ $P&gt;0.10$</td>
<td>$r=0.05$ $P&gt;0.10$</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>$r=0.12$ $P=0.14$</td>
<td>$r=0.21$ $P=0.008$</td>
</tr>
<tr>
<td>Serum calcium-phosphate product</td>
<td>$r=0.10$ $P&gt;0.10$</td>
<td>$r=0.15$ $P=0.07$</td>
</tr>
</tbody>
</table>

Downloaded from http://circ.ahajournals.org/ by guest on April 13, 2017
smoking \((P=0.10)\), larger LV end-diastolic diameter \((P=0.10)\), larger LV end-systolic diameter \((P=0.07)\), and higher serum calcium level \((P=0.08)\).

**Rate of Progression With Selected Coronary Risk Factors**

In patients with a serum cholesterol level >200 mg/dL, the annual reduction in AVA was \(0.14 \pm 0.35 \text{ cm}^2\), compared with \(0.07 \pm 0.19 \text{ cm}^2\) in those with a level \(\leq 200 \text{ mg/dL}\) \((P=0.04)\). The corresponding values for percent reduction in AVA per year were \(10 \pm 21\%\) versus \(5 \pm 15\%\), respectively \((P=0.07)\). The absolute and percent reduction in AVA per year in men compared with women were \(0.12 \pm 0.28 \text{ cm}^2\) versus \(0.05 \pm 0.21 \text{ cm}^2\) \((P=0.19)\) and \(8 \pm 18\%\) versus \(3 \pm 17\%\) \((P=0.11)\), respectively. Rates of progression were not statistically different in those with or those without hypertension or diabetes.

**Rates of Progression at Extremes of Biochemical Values**

To explore the possibility that extremes of biochemical values may have markedly different effects on AS progression, patients were also divided into tertiles based on serum cholesterol, creatinine, and calcium levels, and the lowest and the highest tertiles were compared. The absolute and percentage reduction in AVA were \(0.09 \pm 0.16 \text{ cm}^2\) and \(7.1 \pm 14.1\%\), respectively, in patients at the lowest cholesterol tertile (serum cholesterol \(\leq 165 \text{ mg/dL}\), mean \(133 \text{ mg/dL}\)) compared with \(0.14 \pm 0.29 \text{ cm}^2\) and \(9.4 \pm 20.0\%\) in the highest tertile (serum cholesterol \(\geq 207 \text{ mg/dL}\), mean \(244\)). However, the differences were not statistically significant. The percentage reduction in AVA per year was not significantly different for patients at the lowest and the highest tertiles of serum creatinine \((5.3 \pm 15.2\%\) vs \(9.2 \pm 19.2\%\)) or calcium phosphate product \((3.4 \pm 15.8\%\) vs \(8.2 \pm 19.6\%\)), though there was a greater separation for absolute values. However, it was significantly greater for those in the highest tertile for the serum calcium level compared with those at the lowest tertile \((11.4 \pm 22.0\%\) vs \(3.2 \pm 17.8\%, P=0.05)\).

**Characteristics of Groups at Extremes of Progression**

Table 4 summarizes the characteristics of groups at either end of progression, as judged by the annual reduction in AVA. The rapid progressors (ie, top one third) had a larger initial AVA \((P<0.0001)\), larger LV end-systolic diameter \((P=0.05)\), higher transvalvular velocity \((P=0.001)\), higher LV outflow tract velocity \((P=0.002)\), and higher serum creatinine level \((P=0.04)\). A greater proportion of these patients were on dialysis (11%) compared with the slow progressors (3%), but this difference did not achieve statistical significance \((P=0.14)\).

| TABLE 3. Comparison of Rapid vs Slow Progressors of Aortic Stenosis |
|------------------|------------------|------------------|------------------|
| Variable          | Rapid Progressors | Slow Progressors | \(P\) |
| Age, y            | 70.2±9.9         | 71.9±9.3         | >0.10          |
| Sex, % men        | 83               | 71               | 0.09           |
| Current smoking   | 44%              | 30%              | 0.1            |
| Hypertension      | 52%              | 65%              | 0.12           |
| Diabetes mellitus | 23%              | 20%              | >0.10          |
| Dialysis          | 6%               | 6%               | >0.10          |
| LV outflow tract velocity, m/s | 1.0±0.2         | 0.9±0.18         | 0.07           |
| Peak aortic velocity, m/s | 2.69±0.66       | 2.81±0.69        | >0.10          |
| AVA, cm²          | 1.24±0.43        | 1.11±0.33        | 0.04           |
| Mean systolic gradient, mm Hg | 16±5            | 24±12            | 0.002          |
| LV ejection fraction, % | 54±12           | 57±15            | >0.10          |
| LV end-diastolic dimension, cm | 5.2±0.7         | 4.9±0.9          | 0.11           |
| LV end-systolic dimension, cm | 3.5±0.9         | 3.1±1.2          | 0.1            |
| Ventricular septum, cm | 1.24±0.22       | 1.28±0.23        | >0.10          |
| Posterior left ventricle wall, cm | 1.21±0.20       | 1.17±0.17        | >0.10          |
| Left atrial diameter, cm | 4.4±0.8         | 4.3±0.8          | >0.10          |
| Serum cholesterol level, mg/dL | 187±56          | 186±46           | >0.10          |
| Serum uric acid level, mg/dL | 6.9±2.5         | 6.7±2.7          | >0.10          |
| Serum creatinine level, mg/dL | 1.7±1.7         | 1.5±1.0          | 0.04           |
| Serum phosphate level, mg/dL | 2.7±1.5         | 2.5±1.6          | >0.10          |
| Serum calcium level, mg/dL   | 9.6±0.8          | 9.2±0.8          | 0.08           |
| Serum calcium-phosphate product | 25.2±17.2       | 23.2±15.2        | >0.10          |
Valve Stenosis Behavior in Smokers and Its Correlates
To explore the interaction between smoking and other risk factors, analysis was performed in smokers alone. The effect of various variables on the rate of progression was very similar to that in the whole group except for the fact that thickness of the ventricular septum correlated negatively with the annual rate of AVA reduction ($r = -0.34$, $P = 0.05$). These data are summarized in Table 5.

Multiple Regression Analysis for Predictors of AS Progression
Stepwise multiple regression analysis was carried out to identify the independent predictors of the absolute and percent reductions in AVA per year. A univariate probability value threshold of 0.10 was set for entry into the equation; hence, the sex, smoking status, LV outflow tract velocity, initial AVA, LV end-diastolic diameter, and serum cholesterol, creatinine, and calcium levels were entered as the independent variables. Absolute reduction in AVA per year was independently influenced by initial AVA, smoking, and serum calcium level (cumulative $R = 0.51$), and the percent reduction in AVA per year was independently correlated with LV end-diastolic diameter and serum calcium level (cumulative $R = 0.35$). Sex and serum creatinine levels had a trend toward significance for both and smoking for the latter.

Discussion
This study provides new insights into the factors affecting the rate of AS progression. It raises a strong possibility that smoking, male sex, and elevated serum creatinine, calcium, and cholesterol levels may catalyze AS progression. Many of these findings are new, and some confirm the findings of earlier smaller studies dealing with risk factors for AS progression.2–6 Studies addressing this issue are very limited, though there are elegant studies describing the natural history of AS progression.8,9

Clinical Correlates of AS Progression
In this study, only smoking and male sex were associated with faster AS progression and hypertension; diabetes and age were not. In a study of 120 patients with AS of rheumatic, congenital, or degenerative causes, Mohler et al found only male sex and smoking to be predictors of degenerative AS progression. In a smaller study of 49 patients, Peter et al found older age and the presence of coronary artery disease to be associated with a more rapid increase in AS gradient. In their study of 112 patients, Roger et al did not find age, sex, ejection fraction, or the presence of coronary artery disease to be associated with AS progression, as judged by an increase in the transvalvular velocity obtained by Doppler echocardiography.

Echocardiographic Correlates
In our study, AS progression was slower in severe stenosis, which is also associated with a larger transvalvular gradient. This finding is not new and has been reported by Otto et al and Brener et al. It is tempting to speculate that the stretching effect of a larger gradient in patients with more severe AS retards progression. Higher LV outflow tract velocity, which reflects greater cardiac output, accelerated

### Table 4. Characteristics of Groups at Extremes of Progression Based on Percentage Reduction in AVA per Year

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lower One Third of Progression ($n=57$)</th>
<th>Upper One Third of Progression ($n=57$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70±10</td>
<td>70±10</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>74</td>
<td>81</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Smokers</td>
<td>37%</td>
<td>46%</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67%</td>
<td>57%</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Dialysis</td>
<td>3%</td>
<td>11%</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20%</td>
<td>26%</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>LV end-systolic diameter, cm</td>
<td>3.2±1.2</td>
<td>3.7±1.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Initial AVA, cm$^2$</td>
<td>1.07±0.33</td>
<td>1.42±0.47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in AVA, cm$^2$</td>
<td>−0.09±0.14</td>
<td>0.32±0.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Change in AVA</td>
<td>−8.7±13.5</td>
<td>22.3±17.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic diameter, cm</td>
<td>5.3±0.8</td>
<td>4.9±1.0</td>
<td>0.09</td>
</tr>
<tr>
<td>Peak aortic velocity, m/s</td>
<td>2.4±0.6</td>
<td>2.8±0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>LV outflow tract velocity, m/s</td>
<td>0.9±0.2</td>
<td>1.0±0.2</td>
<td>0.002</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>55±16</td>
<td>52±13</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Serum calcium, mmol/L</td>
<td>2.3±0.2</td>
<td>2.3±0.2</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.4±0.9</td>
<td>2.2±2.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum calcium and phosphate product</td>
<td>5.8±3.8</td>
<td>6.5±4.7</td>
<td>&gt;0.10</td>
</tr>
</tbody>
</table>
AS progression, raising the potential importance of mechanical factors. A higher cardiac output can potentially cause greater trauma to the valve, thus accelerating the inflammatory or degenerative processes in the valve. Also, rapid progressors had larger LV size but similar wall thickness and ejection fraction. Clearly, the effect of LV size, function, and mechanical influences on the aortic valve need further evaluation.

Biochemical Factors
Although AS is seen more often in dialysis patients and seems to be characterized by a more rapid progression,3 the effect of creatinine and calcium in normal patients has not been reported previously. Even after excluding the dialysis patients, these biochemical factors, in a relatively normal range, appeared to affect AS progression. The mechanism of this is unclear. Accelerated AS has also been reported in primary hyperparathyroidism,10 pointing to the importance of the calcium phosphate product, which is also increased in kidney failure. The effect of serum creatinine within the normal range is intriguing and could be either a direct effect on the aortic valve or an indirect effect through other biochemical mediators. The effect of hypercholesterolemia is new, though aortic valve disease occurs in familial hypercholesterolemia and serum triglycerides are associated with AS progression in the bicuspid valve.2,11

Rate of AS Progression
In our study, the mean rate of AS progression was 0.10±0.27 cm² or 7±18% per year and had a very large confidence interval. A wide confidence interval makes prediction of progression in a given patient practically impossible. For example, in a given patient, the reduction in valve area in a year could be as much as 0.64 cm² or 43% of its initial area. This finding is identical to prior published studies.4–6,9

Clinical Implications
This study indicates that the rate of AS progression is unpredictable in a given patient. It can be speculated that modifying the risk factors such as smoking and cholesterol and managing creatinine and calcium phosphate product may be important in AS patients for its secondary prevention. The biochemical and cellular bases of these modifiable risk factors on the progression of AS need further investigation. The relation between degenerative changes in the aortic valve and cardiovascular morbidity and mortality rates also may indicate some common risk factors for both AS and coronary artery disease.12

Study Limitations
This is a retrospective study. The study population is not large enough to exclude the contribution of other risk factors to AS progression. Though the study points to several new risk factors, the mechanisms by which they operate are not clear.

Conclusions
Absolute and percentage reduction in AVA per year in those with AS is greater in those with milder degrees of

<table>
<thead>
<tr>
<th>Variable</th>
<th>AVA Reduction per Year</th>
<th>% AVA Reduction per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>0.15</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Sex</td>
<td>0.16</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.20</td>
<td>0.12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.10</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>LV end-systolic diameter</td>
<td>0.28</td>
<td>0.10</td>
</tr>
<tr>
<td>Initial AVA</td>
<td>0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aorta</td>
<td>0.27</td>
<td>0.08</td>
</tr>
<tr>
<td>Interventricular septum</td>
<td>−0.34</td>
<td>0.05</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>−0.17</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>LV end-diastolic diameter</td>
<td>0.33</td>
<td>0.06</td>
</tr>
<tr>
<td>Peak aortic velocity</td>
<td>−0.27</td>
<td>0.03</td>
</tr>
<tr>
<td>LV outflow tract velocity</td>
<td>0.35</td>
<td>0.006</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>−0.05</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.01</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>0.04</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>0.15</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>0.01</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.20</td>
<td>0.13</td>
</tr>
<tr>
<td>Serum calcium and phosphate product</td>
<td>0.01</td>
<td>&gt;0.10</td>
</tr>
</tbody>
</table>
stenosis and is accelerated in the presence of smoking, hypercholesterolemia, and elevated serum creatinine and calcium levels. These findings may have important implications in gaining further insights into the mechanism of AS progression and in formulating strategies to retard its progression.

References
New Insights Into the Progression of Aortic Stenosis: Implications for Secondary Prevention
Sanjeev Palta, Anita M. Pai, Kanwaljit S. Gill and Ramdas G. Pai

Circulation. 2000;101:2497-2502
doi: 10.1161/01.CIR.101.21.2497
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/101/21/2497

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/