Valvular Heart Disease

Statins but Not Angiotensin-Converting Enzyme Inhibitors Delay Progression of Aortic Stenosis

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Background—Recently, statins and angiotensin-converting enzyme inhibitors (ACEIs) have been shown to slow aortic valve calcium accumulation. Although several studies also suggest that statins may reduce the hemodynamic progression of aortic stenosis (AS), no data are available for ACEIs or the combination of both.

Methods and Results—A total of 211 consecutive patients (aged 70 ± 10 years, 104 females) with native AS, defined by a peak velocity > 2.5 m/s (valve area 0.84 ± 0.23 cm², mean gradient 42 ± 19 mm Hg), with normal left ventricular function and no other significant valvular lesion who were examined between 2000 and 2002 and who had 2 echocardiograms separated by at least 6 months were included. Of these, 102 patients were treated with ACEIs, 50 patients received statins, and 32 patients received both. Hemodynamic progression of AS was assessed and related to medical treatment. Annualized increase in peak aortic jet velocity for the entire study group was 0.32 ± 0.44 m · s⁻¹ · y⁻¹. Progression was significantly lower in patients treated with statins (0.10 ± 0.41 m · s⁻¹ · y⁻¹) than in those who were not (0.39 ± 0.42 m · s⁻¹ · y⁻¹; \( P < 0.0001 \)). This effect was observed both in mild-to-moderate and severe AS. ACEI use, however, did not significantly affect hemodynamic progression \( (P = 0.29) \). Furthermore, ACEIs had no additional effect on AS progression when given in combination with statins \( (0.11 ± 0.42 \) versus \( 0.08 ± 0.43 \) m · s⁻¹ · y⁻¹ for combination versus statin only; \( P = 0.81) \). Cholesterol levels did not correlate with hemodynamic progression either in the group receiving statins or in the group that did not.

Conclusions—ACEIs do not appear to slow AS progression. However, statins significantly reduce the hemodynamic progression of both mild-to-moderate and severe AS, an effect that may not be related to cholesterol lowering.

(Circulation. 2004;110:1291-1295.)

Key Words: stenosis ▪ statins ▪ inhibitors ▪ values

Calcific aortic stenosis (AS) is a progressive disease.¹⁻⁸ Until recently, the concept that calcific aortic valve disease is a degenerative and unmodifiable process basically induced by long-lasting mechanical stress was generally accepted. More recently, however, histopathologic studies have demonstrated that development and progression of calcific AS are based on an active process that shares a number of similarities with athero-sclerosis. Inflammation, lipid infiltration, dystrophic calcification, ossification, platelet deposition, and endothelial dysfunction have been observed in both diseases.⁹,¹⁰ Several studies also have suggested that AS and atherosclerosis have a number of risk factors in common, such as hypercholesterolemia, elevated lipoprotein(a), smoking, hypertension, and diabetes.¹¹⁻¹⁶ In addition, the presence of ACE and angiotensin II, which cannot be found in normal valve tissue, has been demonstrated in sclerotic aortic valves,¹⁷ which suggests a potential role for the renin-angiotensin system in aortic valve lesion pathogenesis. ACE also is found in atherosclerotic lesions,¹⁸ and angiotensin II, with its proinflam-matory effects, is assumed to contribute to the atherosclerotic process.¹⁹,²⁰ These observations raise the important question of whether medical therapies with agents such as statins and ACE inhibitors (ACEIs), which have already been shown to delay the progression of atherosclerosis²¹⁻²³ and to improve the outcome of patients with atherosclerosis,²⁴⁻²⁶ may also affect the progression of AS. Recently, statins²⁷ and ACEIs have been shown to slow aortic valve calcium accumulation.²⁸ Although recent retrospective studies suggest that statins also may slow the hemodynamic progression of AS,²⁹⁻³¹ no data on the effects of ACEIs or the combination of ACEIs and statins on the hemodynamic progression of AS have been reported. Therefore, the aim of the present study was to assess the effects of ACEIs, statins, and their combination on the hemodynamic progression of AS.

Received March 26, 2004; revision received May 24, 2004; accepted May 25, 2004.
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Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000140723.15274.53
**Methods**

**Patient Population**

All patients examined in our outpatient clinic for valvular heart disease between 2000 and 2002 who were found to have a stenotic native aortic valve, as defined by a peak aortic jet velocity >2.5 m/s, and who had ≥2 echocardiographic examinations separated by at least 6 months were included in the present study. Patients with reduced left ventricular function, those with additional hemodynamically significant valve lesions (moderate or severe), and patients with rheumatic valve disease were excluded. According to these criteria, 211 patients (aged 70±10 years; 104 females; aortic valve peak velocity 3.96±0.86 m/s; mean gradient, 42±19 mm Hg; valve area, 0.84±0.23 cm²) were identified. Patient characteristics are shown in the Table.

**Clinical Data**

At study entry, the following clinical data were collected: age, gender, and history of hypercholesterolemia, diabetes mellitus, arterial hypertension (blood pressure >140/90 mm Hg based on the average of repeated measurements), or coronary artery disease (documented previous myocardial infarction or angiographically documented coronary artery stenosis). Furthermore, lipid profiles (including total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels), serum creatinine levels, and blood pressure levels were assessed. Information on the type and dosage of statin as well as ACEI treatment was recorded.

**Echocardiography**

Echocardiography was performed with commercially available ultrasound systems. All patients underwent a comprehensive examination that included M-mode, 2D echocardiography, continuous-wave Doppler, pulsed-wave Doppler, and color Doppler by an experienced echocardiographer. Particular care was taken to record the maximum aortic jet velocity. Aortic valve areas were calculated with the continuity equation.

For assessment of hemodynamic progression, echocardiographic studies separated by at least 6 months were used. When patients had ≥2 serial echocardiograms, hemodynamic progression between the first and last studies was calculated. Annualized changes in aortic jet velocity (m·s⁻¹·y⁻¹), aortic valve area (cm²/y), and peak and mean gradients (mm Hg/y) were calculated by dividing the difference between the first and last measurements by the time between examinations.

**Statistical Analysis**

Continuous variables are expressed as mean±SD. Mean values were compared with the unpaired Student’s t test. ANOVA was used for the comparison of 3 groups. The χ² test was used for evaluation of differences between proportions. A probability value <0.05 was considered to indicate statistical significance. A multiple linear regression analysis was used to determine independent predictors of hemodynamic progression.

**Results**

**Patient Characteristics**

Of the 211 patients, 102 were treated with an ACEI, 50 received a statin therapy, and 32 patients received both. The characteristics of the different patient groups are shown in the Table.

Statin-treated patients were older and more frequently had CAD and hypercholesterolemia than those without this treatment. The following statins were used: simvastatin, 21 patients; atorvastatin, 19; pravastatin, 7; and other, 3. Patients taking ACEIs had slightly higher creatinine levels. They more frequently had hypertension (reason for treatment in all patients) and hypercholesterolemia than did those not receiving an ACEI. The following ACEIs were used: enalapril, 40 patients; lisinopril, 32; ramipril, 10; fosinopril, 8; captopril, 6; and other, 6.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All Patients</th>
<th>No Statin (n=161)</th>
<th>Statin (n=50)</th>
<th>P</th>
<th>No ACEI (n=109)</th>
<th>ACEI (n=102)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, %</td>
<td>49</td>
<td>44</td>
<td>66</td>
<td>&lt;0.01</td>
<td>52</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>70±10</td>
<td>69±11</td>
<td>72±8</td>
<td>&lt;0.05</td>
<td>69±11</td>
<td>70±10</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic valve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jet velocity, m/s</td>
<td>3.96±0.86</td>
<td>3.92±0.86</td>
<td>4.08±0.86</td>
<td>NS</td>
<td>3.95±0.94</td>
<td>3.96±0.77</td>
<td>NS</td>
</tr>
<tr>
<td>Valve area, cm²</td>
<td>0.84±0.23</td>
<td>0.84±0.23</td>
<td>0.82±0.23</td>
<td>NS</td>
<td>0.82±0.23</td>
<td>0.86±0.23</td>
<td>NS</td>
</tr>
<tr>
<td>Peak gradient, mm Hg</td>
<td>66±26</td>
<td>65±29</td>
<td>70±30</td>
<td>NS</td>
<td>66±31</td>
<td>65±26</td>
<td>NS</td>
</tr>
<tr>
<td>Mean gradient, mm Hg</td>
<td>42±19</td>
<td>42±20</td>
<td>41±18</td>
<td>NS</td>
<td>43±21</td>
<td>40±17</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>222±43</td>
<td>219±41</td>
<td>232±48</td>
<td>NS</td>
<td>216±44</td>
<td>228±41</td>
<td>NS</td>
</tr>
<tr>
<td>LDL</td>
<td>142±39</td>
<td>141±39</td>
<td>145±38</td>
<td>NS</td>
<td>138±43</td>
<td>145±34</td>
<td>NS</td>
</tr>
<tr>
<td>HDL</td>
<td>53±16</td>
<td>53±15</td>
<td>56±20</td>
<td>NS</td>
<td>54±17</td>
<td>53±15</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>141±82</td>
<td>132±58</td>
<td>169±130</td>
<td>&lt;0.01</td>
<td>135±63</td>
<td>147±99</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.05±0.23</td>
<td>1.05±0.23</td>
<td>1.06±0.24</td>
<td>NS</td>
<td>1.02±0.20</td>
<td>1.09±0.25</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>27</td>
<td>29</td>
<td>60</td>
<td>&lt;0.05</td>
<td>78</td>
<td>69</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>80</td>
<td>78</td>
<td>86</td>
<td>NS</td>
<td>38</td>
<td>100</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>21</td>
<td>20</td>
<td>21</td>
<td>NS</td>
<td>17</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypercholesterolemia, %</td>
<td>54</td>
<td>40</td>
<td>100</td>
<td>&lt;0.0001</td>
<td>45</td>
<td>63</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.87±0.21</td>
<td>1.88±0.22</td>
<td>1.85±0.19</td>
<td>NS</td>
<td>1.84±0.20</td>
<td>1.91±0.22</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±4.5</td>
<td>26.7±4.3</td>
<td>27.8±4.9</td>
<td>NS</td>
<td>26.1±4.0</td>
<td>28.0±4.8</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>
Hemodynamic Progression in the Entire Study Group

Mean interval between the first and last echocardiographic examination was 24±18 months. Annualized increase in peak aortic jet velocity for the entire study group was 0.32±0.44 m·s⁻¹·y⁻¹. The annualized increase in peak and mean gradients was 11±17 and 8±12 mm Hg/y, respectively. Annualized decrease in aortic valve area was 0.08±0.14 cm²/y.

Statin Therapy and AS Progression

Hemodynamic progression was significantly lower in patients treated with statins (0.10±0.41 m·s⁻¹·y⁻¹) than in those who were not (0.39±0.42 m·s⁻¹·y⁻¹; \(P=0.0001\); Figure 1). This effect was observed both among patients with mild-to-moderate AS and among those with severe AS. Among patients having severe AS, defined by a peak aortic jet velocity >4 m/s at study entry (n=97), hemodynamic progression in the statin-treated patients was 0.03±0.46 m·s⁻¹·y⁻¹ compared with 0.41±0.47 m·s⁻¹·y⁻¹ for the untreated patients (\(P=0.0008\)). Similarly, among patients with mild and moderate AS, defined by a peak aortic jet velocity between 2.5 and 4.0 m/s at entry (n=114), hemodynamic progression was 0.16±0.38 and 0.37±0.38 m·s⁻¹·y⁻¹ for patients with and without statin therapy, respectively (\(P=0.01\)).

Rates of hemodynamic progression were not significantly different for the specific statin types and dosages. Cholesterol levels did not correlate with hemodynamic progression, either in the group receiving statins or in the group that did not (Figure 2). In fact, when we used a multivariate linear regression model that included age, gender, hypercholesterolemia, diabetes mellitus, arterial hypertension, coronary artery disease, ACEI therapy, and statin therapy, only statin therapy was independently related to the progression of AS (\(P=0.0001\)).

ACE Inhibitor Therapy and AS Progression

ACEI therapy did not significantly affect hemodynamic progression. Velocities increased by 0.29±0.44 m·s⁻¹·y⁻¹ and by 0.35±0.44 m·s⁻¹·y⁻¹ in patients with and without ACEI treatment, respectively (\(P=0.29\); Figure 1). Considering the mean progression rate of 0.32±0.44 m·s⁻¹·y⁻¹ and the given sample sizes, the study had the statistical power to detect a difference in mean aortic jet velocity progression of \(>0.2\) m·s⁻¹·y⁻¹ with a probability of 95%.

No significant differences were observed for different types and dosages of ACEIs. Furthermore, rates of hemodynamic progression did not differ between normotensive patients, hypertensive patients receiving an ACEI, and hypertensive patients not receiving an ACEI, with progression rates of 0.36±0.40, 0.29±0.44, and 0.33±0.46 m·s⁻¹·y⁻¹, respectively (\(P=0.64\); Figure 3). In addition, hemodynamic progression did not correlate with systolic or diastolic blood pressure levels in patients receiving an ACEI or in those who did not.

Figure 1. Rate of hemodynamic progression of AS in patients with absence (open bars) or presence (solid bars) of statin therapy and ACEI therapy, respectively.

Figure 2. Hemodynamic progression vs cholesterol level for patients receiving statin therapy (A) and for those not receiving statin therapy (B). Solid line represents regression line. AV-Vel indicates aortic jet velocity.

Figure 3. Rate of hemodynamic progression of AS in normotensive patients, hypertensive patients receiving ACEI therapy, and hypertensive patients not receiving ACEI therapy.
Finally, ACEIs did not have an additional effect on AS progression when given in combination with a statin. Patients receiving the combination of both a statin and an ACEI had a progression rate of 0.11±0.42 m·s⁻¹·y⁻¹ compared with 0.08±0.43 m·s⁻¹·y⁻¹ for patients receiving statins only (P=0.81).

Discussion
AS has become the most common valvular heart disease and the most common heart disease after hypertension and coronary artery disease in Europe and North America. In the elderly, the prevalence of AS has been reported to be between 2% and 9%. Aortic sclerosis, the precursor of AS, has been found in 29% of subjects older than 65 years. Given the poor outcome of AS and the eventual need for cardiac surgery in these patients, AS has become a major health problem and is one of the challenges for cardiology in the new millennium. In the vast majority of patients with AS, the underlying cause is calcific stenosis. This is undoubtedly a chronic progressive disease that begins with thickening and calcification of valve cusps without hemodynamic significance (ie, aortic sclerosis) and eventually ends in heavily calcified, stiff cusps that cause severe valve stenosis. This progression from mild to moderate to severe AS may be very rapid. It has recently become clear that this is not an unmodifiable degenerative process due to mechanical stress but rather an active process that involves (similar to atherosclerosis) inflammation, lipid infiltration, dystrophic calcification, ossification, platelet deposition, and endothelial dysfunction. Thus, current research in AS must focus on clarifying more details of the pathogenetic mechanisms and on developing medical treatment to delay or even avoid the progression of disease. In this context, statins and ACEIs have recently raised particular interest.

Statins and AS
Several studies have demonstrated that AS and atherosclerosis share risk factors such as LDL cholesterol and lipoprotein(a) elevation. These observations have led to the concept that statins that have already been shown to be effective in atherosclerosis might slow the progression of AS. The present study provides further evidence that statins slow the hemodynamic progression of AS and confirms the findings of other retrospective studies. Whether this effect of statin therapy is dependent on cholesterol lowering is controversial. Although Novaro et al have reported an association between AS progression and cholesterol levels, Bellamy and colleagues did not observe such an association. In the present study, the rate of hemodynamic progression was unrelated to cholesterol levels, both among the statin-treated and -untreated patients. These findings further support the hypothesis that the effects of statins at the valvular level may be caused by their pleiotropic or antiinflammatory properties rather than by their cholesterol-lowering effect.

In contrast to previous studies, we also included patients with severe AS in the present study and demonstrated that statins slow the hemodynamic progression in both mild-to-moderate and severe AS. Thus, the beneficial effects of statin therapy are apparently not restricted to the early stage of disease. We have previously shown that a rapid increase in peak aortic jet velocity among patients with severe AS and moderately to severely calcified valves results in a poor outcome. Slowing disease progression in these patients may still beneficially alter their outcome with regard to the development of symptoms and the necessity of surgery. Thus, prospective studies of the effects of statins on hemodynamic progression and on natural history appear to be justified not only in patients with mild-to-moderate AS but also in those with severe AS.

Currently available data on statins in AS can be summarized as follows. There are now 3 large retrospective studies that consistently show that statin therapy is associated with markedly lower hemodynamic progression of AS. Furthermore, 2 studies, including the present study, demonstrated that this effect is independent of cholesterol levels. Finally, the present study shows that this beneficial effect of statins is observed even in patients with severe AS. These findings therefore suggest that statin therapy may be indicated in any patient with AS, regardless of AS severity and cholesterol levels. Given that aortic sclerosis is a precursor of AS, potential benefits of statins in this group deserve further study.

ACEIs and AS
ACE and angiotensin II can be found in sclerotic valves but not in normal aortic valves, which suggests a potential role for the renin-angiotensin system in aortic valve lesion pathogenesis. ACE is also found in atherosclerotic lesions, and angiotensin II is assumed to contribute to the atherosclerotic process via its proinflammatory effects. Thus, ACEIs and angiotensin receptor blockers may affect the pathological process responsible for the development of aortic sclerosis and its progression to AS. ACEIs have been shown to slow calcium accumulation in aortic valves. The present study is the first to evaluate the effects of ACEIs on the hemodynamic progression of AS. However, in contrast to the findings for statin therapy, hemodynamic progression rates did not differ between patients with and without ACEI treatment. It is unlikely that a clinically relevant effect of ACEI might have been missed in the present study, because a difference in mean aortic jet velocity progression of >0.2 m·s⁻¹·y⁻¹ would have been detected with a probability of 95%.

The reason for ACEI treatment was hypertension in all patients, thus resulting in a significantly higher proportion of hypertensive patients in the ACEI-treated group. One might argue that hypertension, with its potentially negative effect on AS progression, may mask a possible benefit of ACEI treatment. However, rates of hemodynamic progression did not differ between normotensive patients, hypertensive patients not receiving an ACEI, and hypertensive patients not receiving an ACEI. Moreover, hemodynamic progression did not correlate with systolic or diastolic blood pressure levels in patients receiving an ACEI or in those who did not. Thus, it is unlikely that a possible negative effect of hypertension may have masked a positive ACEI effect on the progression of AS. Nevertheless, the results of the present study do not preclude the presence of ACEI effects at the valvular level, which may reduce aortic valve calcium accumulation. It cannot be excluded from the results of the present study that the initiation of ACEI therapy at an earlier stage of disease and longer treatment intervals may have positive effects on disease progression.
Study Limitations
The major limitation of this study is its retrospective, non-randomized nature. Nevertheless, the results appear valuable. Statin-treated patients were older and more frequently had coronary artery disease and hypercholesterolemia than those without this treatment. Thus, statin-treated patients who were found to have a lower hemodynamic progression rate actually had a worse risk profile.

Patients receiving an ACEI had only slightly higher creatinine levels and a higher incidence of hypercholesterolemia. As discussed above, it appears unlikely that the higher proportion of hypertensive patients in the ACEI-treated group caused a distortion of the results.

Conclusions
Despite their previously shown effect on aortic valve calcium accumulation, ACEIs do not appear to slow AS progression. However, statins significantly delay hemodynamic progression both in mild-to-moderate AS and in severe AS. This finding may be caused by the pleiotropic or antiinflammatory properties of statins rather than by their cholesterol-lowering effect.

References
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_Circulation_. 2004;110:1291-1295; originally published online August 30, 2004;
doi: 10.1161/01.CIR.0000140723.15274.53

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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