Objective—In patients with severe aortic stenosis (AS), we examine the association between: (1) the content of oxidized LDL (oxLDL) in the aortic valve and the degree of inflammation and remodeling; (2) The proportion of small dense LDL particles in the plasma and the presence of oxLDL in the valve along with hemodynamic progression of valve stenosis.

Methods and Results—We have examined 102 explanted AS valves. Tissue remodeling, inflammation, and accumulation of oxLDL were determined. A complete plasma lipid profile including the measurement of the relative proportion of small low-density lipoprotein (%LDL \textsubscript{255Å}) was obtained. Valves with higher oxLDL content had a significantly higher density of inflammatory cells, expression of tumor necrosis factor (TNF)-α, and increased tissue remodeling score. The %LDL \textsubscript{255Å} was significantly associated with oxLDL score within the aortic valve. In a subset of 59 patients in whom stenosis progression was measured, the %LDL \textsubscript{255Å} correlated with the annualized peak gradient ($r=0.29; P=0.04$).

Conclusion—Increased proportion of circulating small dense LDL particles is associated with faster progression rate of stenosis and greater accumulation of oxLDL in the aortic valve. These findings suggest that therapeutic interventions aimed at lowering the production of small dense LDL particles in patients with AS might represent a potentially interesting therapeutic avenue. (Arterioscler Thromb Vasc Biol. 2008;28:187-193.)

Key Words: aortic stenosis ■ oxidized low-density lipoproteins ■ small size low-density lipoprotein particles
Methods

Patients and Tissue Collection

We examined 102 AS valves that were explanted from patients at the time of aortic valve replacement. Patients with an aortic regurgitation grade \(>2^+\), a history of rheumatic disease, endocarditis, or an inflammatory disease were excluded. Samples were taken at the time of surgery. Two segments were partially decalcified in Cal-Ex (Fisher, Nepean) for 24 hours, and then one segment was fixed in formaldehyde 10% for histological processing and the other one was embedded in optimum cutting temperature (OCT) compound (TissueTek, Miles Laboratories) and frozen in liquid nitrogen (LN\(_3\)) for immunohistochemical analyses.

Histological Analysis and Tissue Remodeling Score

Decalcified and fixed tissues were processed for routine paraffin embedding. Valve samples were excised vertically to the base at the midpoint. Five-\(\mu\)m-thick sections were obtained and stained with hematoxylin-eosin (H&E). Histological sections were analyzed and the degree of valvular tissue remodeling and calcification was assessed using a scoring system adapted and modified from Warren et al.\(^{16}\) Grade 1: mild fibrous thickening, structural integrity of the cusps is maintained; Grade 2: moderate valve thickening and early nodular calcification with preservation of the fibrosa; Grade 3: severe thickening with many calcified nodules and a distorted fibrosa; Grade 4: severe thickening and distortion with many calcified nodules, important fibrosis, and destruction of most structural components with disruption of elastic tissue. The remodeling score was attributed by an experienced cardiovascular pathologist (C. Couture) blinded to clinical data and to immunohistochemical analyses.

Immunohistochemical Analysis

Immunohistochemistry was performed in cryostat sections. Immunohistochemical analysis of cell markers was performed using the following antibodies: a mouse anti–phages CD68/H11001 (Cedarlane), anti-T cells CD3/H11001 (Biomed). The presence of TNF-\(\alpha\) and oxLDL were also detected using immunohistologic analysis with the following antibodies: a mouse anti–TNF-\(\alpha\) (Abcam) and a polyclonal (rabbit) antibody anti-oxLDL (Calbiochem). Slides were then incubated with a biotin-conjugated anti-mouse or an anti-rabbit antibody immunoglobulin antibody (Jackson Immuno Research) followed by HRP-conjugated streptavidin and ABC substrate (Dako). Tissue sections were counterstained with hematoxylin. Mouse serum was used as a negative control in immunohistologic experiments.

Quantitative Assessment of Inflammation

To assess the numbers of leukocytes (CD45\(^+\)), monocytes/macrophages (CD68\(^+\), and T cells (CD3\(^+\)), representative regions rich in cells were detected in each section and the number of cells was counted by two observers blinded to clinical results. The cells were counted at 400\(\times\) in triplicates, and a mean value was attributed to each valve. Data were reported as the average number of cells per 400\(\times\) field. To assess the presence of TNF-\(\alpha\) and oxLDL in the aortic valve, a semi-quantitative score from 0 to 3 was used. Score 0 was given when there was no evidence of specific staining for oxLDL or TNF-\(\alpha\), whereas scores 1, 2, or 3 were given, respectively, when less than 25%, 25% to 50%, and more than 50% of the valve area was specifically immunostained.

Lipid Profile

Overnight fasting plasma was collected and immediately processed by the laboratory for the measurement of glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides. After centrifugation, one plasma specimen was kept and stored at \(-80^\circ\)C until measurement of LDL particle size as previously described.\(^{17}\) Briefly, LDL particle size was determined using a non-denaturing 2% to 16% polyacrilamide gradient gel electrophoresis. LDL particle size was extrapolated from the migration of standards of known diameters. In each gel, 3 standards each containing 4 bands were loaded. These plasma standards were previously calibrated with other standards of known diameters such as ferritin, thyroglobulin, and 380A latex bands. LDL peak particle size corresponded to the estimated diameter of the major peak on the gel for each patient. The relative proportion of small \((<255\AA)\) LDL-C particles \((%LDL_{255\AA})\) was determined by computing the relative area of the densitometric scan on the gel.

Doppler Echocardiography

All patients underwent a comprehensive Doppler echocardiographic examination preoperatively. Doppler echocardiographic measurements included the left ventricular stroke volume and transvalvular gradients using modified Bernoulli equation. In a subset of 59 patients in whom 2 or more serial echocardiograms separated by at least 6 months were available, the hemodynamic progression of stenosis was determined. Annualized changes in peak gradients (mm Hg/year) were calculated by dividing the difference between the first and the last measurements by the time between examinations.

Statistical Analysis

Patients were classified into 4 groups according to their oxLDL score (0, 1, 2, or 3). Continuous data were expressed as mean\(\pm\)SEM and compared using a 1-way ANOVA to test the effect of group. Post hoc Tukey analyses were done when the probability value of the ANOVA was \(<0.05\). Categorical data were expressed as a percentage and compared with the chi-square test. Correlations between variables were determined using Spearman coefficients. Multiple linear regression analysis was used to identify the independent correlates of annualized peak transvalvular gradient and \(%LDL_{255\AA}\). A probability value \(<0.05\) was considered significant. Statistical analysis was performed with a commercially available software package JMP IN 5.1.

Results

Patients

The characteristics of patients are presented in Table. The mean age of the patients was 68\(\pm\)1 years, and 63% were males. The most common comorbidities in this sample were high blood pressure (60%) and diabetes (24%). The mean preoperative peak transvalvular gradient was 73\(\pm\)2 mm Hg. Macroscopic examination of AS valves revealed that 25% of the aortic valves were bicuspid; all showed evidence of marked thickening and important calcification.

The presence of oxLDL was detected in 93 (91%) of the studied valves with the following distribution: score 1 \((n=39; 38\%)\), score 2 \((n=40; 39\%)\), and score 3 \((n=14; 14\%)\). Immunostaining for oxLDL was found in cellular-rich regions and at the proximity of calcification areas. Patients were stratified into 4 groups according to the oxLDL score (Table).

Plasma Lipid Profile and Valvular oxLDL Content

Age, gender, prevalence of traditional risk factors, and treatment with statins were not significantly different between groups (Table). The comparison of the plasma lipid profile revealed no significant difference between groups for LDL-C and HDL-C. However, the triglyceride level was higher \((P\text{ ANOVA}=0.02\) and the \(%LDL_{255\AA}\) was increased in the patients with higher oxLDL scores \((P\text{ ANOVA}=0.04; \text{ Figure 1A and 1B})\). The \(%LDL_{255\AA}\) correlated with the body mass index \((r=0.19; P=0.03)\), waist circumference \((r=0.21;\)
P = 0.02), and plasma triglyceride level (r = 0.30; P = 0.005), whereas there was no significant correlation with LDL-C levels. There was no significant association between the %LDL<sub>255Å</sub> and the use of statins. The %LDL<sub>255Å</sub> was significantly (P = 0.01) lower in the patients with an oxLDL score of 0 (26.5 ± 6.9%) compared with those with an oxLDL score of 3 (50.9 ± 6.9%; Figure 1A). The %LDL<sub>255Å</sub> correlated significantly with the density of leukocytes (r = 0.45; P = 0.0001) in the aortic valve. After correction for age, gender, triglyceride levels, the %LDL<sub>255Å</sub> was found an independent predictor of higher valvular oxLDL score (P = 0.035). In addition, the %LDL<sub>255Å</sub> but not triglyceride level was an independent predictor of the valvular density of leukocytes (r² = 0.18; P = 0.009).

### Table. Demographic, Clinical Laboratory, and Immunohistochemical Data According to the Valvular Oxidized LDL Score

<table>
<thead>
<tr>
<th>Ox-LDL Score</th>
<th>All Patients (n=102)</th>
<th>Grade 0 (n=9)</th>
<th>Grade 1 (n=39)</th>
<th>Grade 2 (n=40)</th>
<th>Grade 3 (n=14)</th>
<th>P ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68±1</td>
<td>64±4</td>
<td>70±2</td>
<td>68±2</td>
<td>68±3</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>63</td>
<td>44</td>
<td>59</td>
<td>67</td>
<td>76</td>
<td>NS</td>
</tr>
<tr>
<td>Active smoking, %</td>
<td>9</td>
<td>22</td>
<td>3</td>
<td>10</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>60</td>
<td>56</td>
<td>59</td>
<td>62</td>
<td>62</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>24</td>
<td>22</td>
<td>23</td>
<td>28</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Peak gradient, mm Hg</td>
<td>73±2</td>
<td>72±7</td>
<td>68±3</td>
<td>75±3</td>
<td>80±5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean gradient, mm Hg</td>
<td>44±1</td>
<td>42±5</td>
<td>41±2</td>
<td>44±2</td>
<td>49±3</td>
<td>NS</td>
</tr>
<tr>
<td>Bicuspid valve, %</td>
<td>25</td>
<td>22</td>
<td>21</td>
<td>31</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Statin treatment, %</td>
<td>70</td>
<td>63</td>
<td>67</td>
<td>69</td>
<td>85</td>
<td>NS</td>
</tr>
<tr>
<td>ACE treatment, %</td>
<td>29</td>
<td>25</td>
<td>25</td>
<td>36</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>92±2</td>
<td>81±7</td>
<td>91±3</td>
<td>93±3</td>
<td>98±6</td>
<td>NS</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>5.5±0.1</td>
<td>5.1±0.3</td>
<td>5.5±0.2</td>
<td>5.6±0.2</td>
<td>5.6±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.3±0.11</td>
<td>4.60±0.30</td>
<td>4.17±0.17</td>
<td>4.35±0.17</td>
<td>4.44±0.30</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.36±0.09</td>
<td>2.53±0.30</td>
<td>2.23±0.14</td>
<td>2.46±0.14</td>
<td>2.35±0.25</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.33±0.03</td>
<td>1.39±0.11</td>
<td>1.31±0.05</td>
<td>1.37±0.05</td>
<td>1.24±0.09</td>
<td>NS</td>
</tr>
<tr>
<td>LDL peak particle size, Å</td>
<td>258.6±0.6</td>
<td>259.5±2.1</td>
<td>257.9±1.1</td>
<td>259.3±0.9</td>
<td>257.0±2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.44±0.08</td>
<td>1.60±0.24</td>
<td>1.34±0.11</td>
<td>1.31±0.11</td>
<td>2.02±0.20</td>
<td>0.02</td>
</tr>
<tr>
<td>%LDL&lt;sub&gt;255Å&lt;/sub&gt;</td>
<td>38.9±2.2</td>
<td>26.5±6.9</td>
<td>43.1±3.6</td>
<td>35.9±3.2</td>
<td>50.9±6.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Leucocytes CD45+</td>
<td>27±3</td>
<td>6±8</td>
<td>23±5</td>
<td>29±4</td>
<td>39±7</td>
<td>0.02</td>
</tr>
<tr>
<td>Macrophages CD68+</td>
<td>11±2</td>
<td>3±1</td>
<td>8±2</td>
<td>11±2</td>
<td>28±7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T lymphocytes CD3+</td>
<td>2±1</td>
<td>1±1</td>
<td>1±1</td>
<td>5±2</td>
<td>7±3</td>
<td>0.03</td>
</tr>
<tr>
<td>TNFα score</td>
<td>1.5±0.1</td>
<td>1±0.3</td>
<td>1.3±0.1</td>
<td>1.7±0.2</td>
<td>1.8±0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Remodeling score</td>
<td>3±0.1</td>
<td>2.5±0.3</td>
<td>2.8±0.1</td>
<td>3.3±0.1</td>
<td>3.3±0.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Relation Between Valvular OxLDL, Inflammation, and Tissue Remodeling**

AS valves with the highest oxLDL score (3) had a significantly higher density of leukocytes (CD45+: P ANOVA = 0.02; r = 0.39; P = 0.0001), macrophages (CD68+: P ANOVA < 0.0001; r = 0.38, P = 0.0001), and T cells (CD3+: P ANOVA = 0.03; r = 0.27, P = 0.01), compared with valves with lower oxLDL (Figures 2 and 3). In addition, expression of TNFα was increased in patients with highest oxLDL score. Semiquantitative scores for TNF-α were 1.0±0.3, 1.3±0.1, 1.7±0.2, and 1.8±0.2 for valvular oxLDL scores of 0, 1, 2, and 3, respectively (P ANOVA = 0.01; r = 0.32, P = 0.001; Figures 2 and 3). Furthermore, tissue remodeling score was significantly increased in valves with the higher oxLDL score (P ANOVA = 0.04; r = 0.30, P = 0.007; Table). In addition, we found a significant association between the remodeling score and TNFα (P ANOVA = 0.04; r = 0.20 P = 0.01).

In the subset of 25 patients with a bicuspid aortic valve, there was a significant correlation between valvular oxLDL score and: CD45 (r = 0.57; P = 0.004), CD68 (r = 0.49, P = 0.01); and tissue remodeling score (r = 0.68, P = 0.001). However, the other associations with CD3, TNFα, and the %LDL<sub>255Å</sub> did not reach statistical significance.

After adjusting for age, gender, statin therapy, triglyceride level, %LDL<sub>255Å</sub>, and the valve morphology (ie, bicuspid versus tricuspid AV), oxLDL remained significantly associated with the presence of: CD45: (r² = 0.13, P = 0.02), CD68 (r² = 0.19, P = 0.0003), CD3: (r² = 0.15, P = 0.01), TNFα (r² = 0.17, P = 0.002), and with the remodeling score: (r² = 0.12, P = 0.01).

**Relation Between Small LDL Particles and Preoperative Stenosis Progression**

In the subset of 59 patients for whom stenosis progression was documented, we found that the %LDL<sub>255Å</sub> correlated with the annualized peak transvalvular gradient (r = 0.29; P = 0.04). When the %LDL<sub>255Å</sub> was dichotomized according to the median value (36%), the mean progression rate of peak gradient was 7 ± 1 mm Hg/year in patients with a %LDL<sub>255Å</sub> ≤ 36% and 11 ± 1 mm Hg/year in patients with a higher %LDL<sub>255Å</sub> (P = 0.02). There was no significant correlation.
between HDL-C, LDL-C, or triglyceride level and progression of the stenosis (P<0.05) When adjusting for age, gender, triglyceride level, statin therapy, and the morphology of the aortic valve (ie, bicuspid versus tricuspid), the %LDL remained significantly associated with the progression rate of peak gradient (r²=0.15, P=0.03).

Discussion

The most important contribution of this study was to reveal a significant association between the proportion of small LDL particles in the plasma and (1) the progression rate of the valvular stenosis, and (2) the content of oxLDL and the degree of inflammation in the aortic valve. Our results obtained in large number of explanted valves also show that oxLDL is present in a high proportion (91%) of the valvular tissue of patients with severe AS, and that it is associated with increased inflammatory activity and valvular remodeling. These findings provide support to the hypothesis that the accumulation of oxLDL within the valve leaflets contribute to the inflammatory and calcifying processes leading to AS, and that atherogenic dyslipidemia characterized by a high proportion of small dense LDL particles in the plasma may enhance the accumulation of oxLDL in the valve, and thus the progression of calcific aortic valve disease.

Relation Between oxLDL and Valvular Inflammation

Calcific AS is now considered as a cellular-mediated process in which activation of the inflammatory pathways plays a critical role. Lipid infiltration, and the presence of inflammatory cells along with cytokines within AS valves, suggest that a process related to atherosclerosis contributes to the development of this disease. It is believed that initiation of the inflammatory process in the aortic valve might be driven by lipid accumulation within the valve leaflets. As previously reported by Olsson et al in 6 AS valves, the results of the present study confirm the presence of oxLDLs in calcific AS valves and their colocalization with macrophages and T cells, thus suggesting that the inflammatory process is closely linked to the presence of oxidatively modified lipids. oxLDL participate to the recruitment of macrophages and the formation of foam cells which in turn produce TNF-α. Accordingly, increased oxLDL score was associated with higher expression of TNF-α.

Relation Between OxLDL and Valvular Tissue Remodeling and Calcification

Calcification and fibrosis are prominent features of AS, leading to leaflet thickening and stiffening and eventually to the obstruction of the valvular orifice. Histological studies have demonstrated that calcification is present in early stages of the disease and colocalizes with lipoproteins and inflammatory cells. In the present study, higher valvular oxLDL expression was associated with increased tissue remodeling score, suggesting that oxLDL could be involved in the fibrocalcification of the aortic valve. To this effect, in vitro studies in isolated vascular cells have reported that oxLDL and TNF-α are strong inducers of calcification with phenotypic transformation of cells toward bone-forming cells.

Origin of Valvular oxLDL

The accumulation of oxLDL in the aortic valve might be the result of (1) an infiltration of plasma LDL particles within the valvular tissue and then an in situ oxidation of these particles; (2) an infiltration of circulating oxLDL into the valvular tissue.

It has been shown that small dense LDL particles remain in circulation for a longer period of time and have an increased ability to infiltrate tissue and to be oxidized rapidly. Thus, it would be plausible that these properties of small LDL particles explain, at least in part, the association we found between the amount of circulating small LDL subfraction and: the valvular content of oxLDL content and the progression of calcific aortic valve disease.
sion of the stenosis. Weiss et al. recently reported the presence of a high content of superoxide in the valve tissue of mice with advanced AS. Their results suggest that at least some oxLDL may be formed in situ, thus implicating local cellular processes, as initiators of valve calcification.

In the present study, the fact that the proportion of small dense LDL particles was an independent predictor of stenosis progression after adjustment for other risk factors and medications, further support the contribution of this factor to the pathogenesis of AS.

Clinical Implications
From the associations reported in the present study, it is difficult to confirm that there is a causative relationship between small dense LDL particles in the plasma and the progression of AS. Our results nonetheless raise the hypothesis that interventions targeting factors involved in the production of small dense LDL particles and in the oxidative transformation of lipids within the aortic valve might contribute to decrease valvular inflammation and remodeling process and thus reduce disease progression. As shown in the present study and in previous studies, the proportion of small LDL particles does not correlate with LDL-C levels, whereas it correlates with plasma triglyceride levels. It is indeed believed that triglyceride enrichment of lipoproteins is a key event leading to smaller LDL particles. It is possible that therapeutic interventions aimed at reducing triglyceride level or the proportion of small size LDL particles might be able to slow disease progression in patients with AS. Statins are presently the drugs that are currently under the most scrutiny for the treatment of AS. A prospective study has demonstrated that patients with mild to moderate AS and high LDL-C levels treated with rosuvastatin had a lower stenosis progression compared with patients with similar degree of AS but normal LDL-C level and not being treated with statins. However, a randomized study using atorvastatin has failed to prevent stenosis progression in patients with moderate or severe calcific AS. These results as well as those of other recent studies suggest that beyond LDL-C level, other factors such as the size of LDL particles may also influence disease progression. However, several studies have reported that statins have no or minimal effect on the size of LDL particles. Other classes of drugs, which have been shown to significantly increase the size of LDL particles (eg, fibrates, niacin, thiazolidinediones), could thus be envisioned to alter AS progression. Further mechanistic and interventional studies are however necessary before the size of LDL particles or triglyceride levels could be considered as new targets of therapy in calcific aortic valve disease.

Limitations of the Study
Expression of TNF-α and oxLDL were determined from a semiquantitative scoring system and were not validated by quantitative techniques, thus potentially decreasing precision. However, the utilization of standardized scoring systems for the quantification of these factors, the quantitative analysis of the density of inflammatory cells, and the large number of valves analyzed in this study further reinforce the robustness of the findings.
of our observations and conclusions. Furthermore, the quantitative analysis of LDL particle size has contributed to obtain some mechanistic insights regarding the factors involved in accumulation of oxLDL in the valve and in disease progression.

This cross-sectional study has some inherent limitations insofar as it included patients with an advanced pathological process necessitating an aortic valve replacement. In light of this inherent limitation, the results and conclusions of this study should be restricted to end-stage AS and cannot be directly extrapolated to the whole spectrum of the disease process. Moreover, the true magnitude of the contributions of oxLDL to the pathogenesis of AS cannot be appreciated from the data of this study. In fact, it is quite likely that patients arrive at the final common end point of severe aortic valve disease as a result of diverse pathophysiological processes; some of which involve oxLDL-related cellular inflammation and some of which do not. To this effect, 9 patients (9%) included in this study had no oxLDL detected in their valves and still had severe AS, suggesting that other mechanisms contributed to the pathogenesis of AS in these patients.

Conclusion

Increased proportion of small dense LDL particles in the plasma is associated with faster progression rate of the valvular stenosis and greater accumulation of oxLDL in the aortic valve. In turn, the accumulation of oxLDL is associated with increased inflammation and fibro-calcific remodeling within the aortic valve. These results support the hypothesis that the production of small dense LDL particles may contribute to the accumulation of oxidatively-transformed lipids in the aortic valve and may thereby enhance the inflammation and calcification of the valve tissue. Further studies are now needed to determine whether therapeutic interventions aimed at lowering the production of small dense LDL particles or at reducing the in situ oxidation of LDL might be efficient to slow the progression of calcific AS.

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Disclosures

None.

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