Lupus Atherosclerosis Prevention Study (LAPS)

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ABSTRACT

Background Cardiovascular disease is one of the major causes of death in systemic lupus erythematosus (SLE). A study was undertaken to investigate whether treatment with statins would reduce subclinical measures of atherosclerosis over a 2-year period.

Methods 200 patients with SLE without clinical cardiovascular disease were randomised to receive atorvastatin 40 mg daily or an identical placebo. At baseline and after 2 years of follow-up, helical CT scanning (for coronary artery calcium) and carotid duplex (for intima media thickness/plaque) were performed. Patients were seen for measures of disease activity at 1 month, 3 months and quarterly thereafter. The primary outcome variable was change in coronary artery calcium.

Results At baseline, 43% had coronary artery calcium. At 2 years there was no significant difference between the groups in progression of coronary artery calcium, carotid intima media thickness or carotid plaque. There was no significant difference between the groups in disease activity, measures of inflammation or endothelial cell activation.

Conclusion This study provides no evidence that atorvastatin reduces subclinical measures of atherosclerosis or disease activity over 2 years in patients with SLE. In fact, it does not appear to reduce biochemical measures of inflammation. The anti-inflammatory effects of statins observed in the general population were not replicated in this SLE clinical trial. Clinical trials.gov (NCT 00120887).

INTRODUCTION

Atherosclerosis is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE). 1 2 3 Accelerated atherosclerosis in SLE is attributed both to an increase in traditional cardiovascular risk factors 4 and to the inflammatory effect of SLE itself. There is a bimodal pattern of mortality in SLE, with early deaths caused more by infection and late deaths caused more by cardiovascular disease. 5 In one study the risk of myocardial infarction in women with SLE aged 35–44 years was increased 50-fold over Framingham controls. 6 Traditional cardiovascular risk factors do not completely explain the increased risk, 7 8 suggesting that—as in the general population 9—inflammation plays a role. Non-invasive measures of subclinical atherosclerosis have advanced the study of atherosclerosis in SLE. Both coronary artery calcification 10 11 and carotid atherosclerosis have been studied in SLE 12 13.

Statins reduce the progression of atherosclerosis in the general population 14 by reduction of low-density lipoprotein (LDL) cholesterol and also by pleiotrophic anti-inflammatory effects including decreasing adhesion molecules, reducing tissue factor expression, reducing inflammatory cytokines, increasing fibrinolytic activity and reducing expression of class II major histocompatibility complex antigens. 15 Furthermore, statins may prevent endothelial cell activation induced by antiphospholipid antibodies 16 which occurs in up to 50% of patients with SLE.

The anti-inflammatory effect of statins may have benefit in some autoimmune diseases. In 116 patients with rheumatoid arthritis, atorvastatin reduced disease activity compared with placebo. 17 In multiple sclerosis, treatment with atorvastatin reduced the number and volume of gadolinium-enhancing lesions in brain MRIs. 18 Other studies with simvastatin and lovastatin have also shown beneficial effects of statins in multiple sclerosis. 19 20

Statins have not been widely studied in SLE. In a small study of 41 patients with SLE designed to study dose-effectiveness and statin tolerability, 10 or 40 mg pravastatin per day led to a reduction in total cholesterol of 16–21% and in LDL-cholesterol of 24–35%. However, it did not reduce C-reactive protein (CRP). 21 Rarely, statins may cause drug-induced lupus. 22 23 Given the high burden of atherosclerotic disease in SLE and the potential anti-inflammatory effects of statins, we sought to determine if a statin could reduce progression of subclinical atherosclerosis and/or could reduce disease activity in SLE.

METHODS

Inclusion/exclusion criteria

The inclusion criterion was a clinical diagnosis of SLE. In addition, 95% of patients had four or more American College of Rheumatology (ACR) criteria and the remaining patients had three. Patients aged >18 years were included. Patients were excluded if they had a known prior atherosclerotic event, were pregnant, had chronic liver disease, triglycerides >500 mg/dl or LDL-cholesterol >190 mg/dl, creatine kinase (CK) >1.5 times the upper limit of normal or liver function tests (LFT) >2 times the upper limit of normal. None of the patients was on statins in the 3 months prior to the study.

Study design

This was a randomised double-blind placebo controlled trial of atorvastatin 40 mg versus matching placebo. At baseline, coronary artery calcium was assessed by helical CT scanning. Carotid intima media thickness (IMT) and carotid plaque were assessed by carotid duplex. After baseline measures were completed, the patients were randomised into the two treatment groups. The randomisation was stratified by the presence or absence of coronary artery calcium at baseline to ensure that the study groups were balanced with respect to this variable. Disease activity was assessed at baseline and quarterly using the Safety of Estrogens
of the common carotid artery (the 1 cm segment proximal to the bifurcation) by a single reader using an automated edge detection system. The mean IMT of this 1 cm segment was measured on two separate images of the left and the right common carotid artery at the peak of the R wave on a simultaneous ECG tracing. The mean of these four measurements was used as the IMT. This location was chosen because of its demonstrated reproducibility compared with measurements of carotid IMT at other sites. Each ultrasound examination was performed as an independent study without knowledge of the previous IMT results. Both patients and providers were blinded to the IMT results until the 2-year follow-up examination was completed. Carotid plaque was defined as focal protrusion into the lumen with a thickness at least 50% greater than the surrounding IMT.

Safety monitoring
The Data Safety Monitoring Board reviewed the study at the onset and throughout the trial. Safety monitoring of LFTs and creatine kinase (CK) was performed at 1 month and then at the quarterly visit. If the LFTs or CK were 3× the upper limit of normal, the drug/placebo was stopped and resumed at 20 mg (half the original dose) after normalisation. If the LFTs or CK were 2× normal they were rechecked monthly until they fell below 2× the upper limit of normal.

Outcome measures
There were two primary outcome measures. For atherosclerosis, the primary outcome measure was reduction in the progression of coronary artery calcification. Coronary artery calcification was assessed by helical CT scanning with a Siemens Volume Zoom Scanner (Siemens Medical Solutions, Malvern, Pennsylvania, USA) using a 2.5 mm collimation and a slice width of 3 mm. Data were reloaded into a Siemens Leonardo workstation using the Siemens calcium scoring software. Coronary artery calcification was quantified using a standard scoring system available as part of the scanner software package. Coronary calcification scores were calculated using Agatston scoring.

Carotid duplex scanning
High-resolution B-mode ultrasound was performed at baseline and at 24 months to image the right and left common carotid arteries using a single ultrasound machine (Philips Medical Systems Sonos 5500) with a linear array 8 MHz scan head with standardised image settings including resolution mode, depth of field, gain and transmit focus. Digital imaging and communications in medicine images from a diastolic frame of the cine-loop recording were electronically stored and transferred via optical disk to an offline workstation for analysis. Carotid IMT was measured between the lumen intima and media–adventitia interfaces of the far wall of the common carotid artery (the 1 cm segment proximal to the bifurcation) by a single reader using an automated edge detection system. The mean IMT of this 1 cm segment was measured on two separate images of the left and the right common carotid artery at the peak of the R wave on a simultaneous ECG tracing. The mean of these four measurements was used as the IMT. This location was chosen because of its demonstrated reproducibility compared with measurements of carotid IMT at other sites.

Figure 1  Study consort diagram.
of subclinical atherosclerosis as assessed by the coronary artery calcium score. Owing to the fact that the distribution of this score was skewed, we based our analysis on the log-transformed score. Secondary atherosclerosis outcomes included reduction in progression of IMT and carotid plaque. For disease activity, the primary outcome was improvement in the SELENA SLEDAI which was measured at all clinic visits in the 2 years preceding the study and during the 2 years of the clinical trial.24

**Statistical methods**

Paired t tests were used to assess the statistical significance of observed changes in indicators of subclinical atherosclerosis and other variables. To compare the intervention groups with respect to changes in these variables, an ANCOVA model was used with change as the dependent variable and the baseline level as a covariate. To assess the impact of the intervention on disease activity we used a mixed effects regression model to account for the correlation between repeated SELENA SLEDAI measures for each patient.

**Power of the study**

Using the estimated variance from the completed study, we calculated that a study of this size had 80% power to detect a difference between the groups if the factor by which coronary artery calcium (CAC+1) increased in the placebo group over the 2-year period was 55% higher than the factor by which coronary artery calcium (CAC+1) increased in the atorvastatin group.

**RESULTS**

**Patients**

Figure 1 shows the numbers of patients with SLE who consented, were randomised and who completed follow-up. Two hundred patients were enrolled and randomised. The patients had a mean (SD) age of 44.7 (11.3) years (range 18–78), 92% were female, 61% Caucasian, 33% African-American, 2% Asian and 2% Hispanic. Cumulative ACR revised classification criteria for SLE29 30 included malar rash 63%, discoid rash 23%, photosensitivity 60%, oral ulcers 54%, arthritis 80%, serositis 50%, renal disorder 40%, neurological disorder 9%, immunological disorder 75% and ANA positivity 97%. The groups were similar with respect to the baseline variables (table 1).

**Baseline lipids**

Patients with elevated fasting triglycerides >500 mg/dl or LDL-cholesterol >190 mg/dl were excluded from participation in the trial. At baseline the mean (SD) total cholesterol in enrolled patients was 186 (38) mg/dl with 34% having total cholesterol levels >200 mg/dl. The mean (SD) LDL-cholesterol was 103 (31) mg/l with 48% having LDL >100 mg/dl. None of the patients receiving statins at baseline or prior to the study.

**Baseline atherosclerosis measures**

At baseline 57% had no coronary artery calcium, 22% had an Agatston score of >0–10, 12% had 11–99 and 8% had ≥100 AU. At baseline the IMT was 0.4–0.5 mm in 23%, 0.5–0.6 mm in 27%, >0.6–0.7 mm in 24% and >0.7–1.0 mm in 12%. At baseline, 17% had carotid plaque.

**Two-year atherosclerosis measure results**

There were no statistically significant differences between the groups with respect to changes in coronary artery calcium score (table 2). Table 3 shows the raw score distribution of coronary artery calcium scores as well as comparing the two groups using raw scores. There was a greater increase in coronary artery calcium score in the placebo group, but a Wilcoxon non-parametric test yielded a non-significant p value (p=0.25). We did an additional analysis using a five-group categorisation of Agatston scores (0.1–10,11–100,101–400,401+). The two treatment groups were still similar with respect to change in categories (p=0.44) based on the χ2 test. There was also no significant difference between the groups with respect to change in carotid IMT (table 2). In a post hoc analysis there was a difference in favour of atorvastatin (p=0.014) in the proportion in whom carotid IMT improved, stayed the same or got worse by group and baseline level (table 4).
### Table 2  Changes in indicators of atherosclerosis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean at baseline</th>
<th>Mean after 2 years</th>
<th>Mean change</th>
<th>p Value for change</th>
<th>Difference in change, statin minus placebo(95% CI)</th>
<th>p Value for difference between groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log, (coronary artery calcium score + 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1.16</td>
<td>1.24</td>
<td>0.08</td>
<td>0.52</td>
<td>-0.08 (−0.39 to 0.23)</td>
<td>0.62</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.19</td>
<td>1.35</td>
<td>0.15</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid intima media thickness (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>0.59</td>
<td>0.66</td>
<td>0.07</td>
<td>&lt;0.0001</td>
<td>-0.02 (−0.05 to 0.01)</td>
<td>0.24</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.57</td>
<td>0.66</td>
<td>0.09</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This table is based on the 96 patients given atorvastatin and the 91 patients given placebo for whom there were both baseline and follow-up measures.

† Based on an ANCOVA model controlling for baseline level.

### Table 3  Number (%) of patients with various degrees of change in coronary artery calcium (CAC) score by group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Decrease of &gt;30 points</th>
<th>Decrease of 1–30 points</th>
<th>No change</th>
<th>Increase of 1–30 points</th>
<th>Increase of &gt;30 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>3 (3%)</td>
<td>18 (19%)</td>
<td>49 (51%)</td>
<td>14 (15%)</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0 (0%)</td>
<td>14 (15%)</td>
<td>49 (54%)</td>
<td>12 (13%)</td>
<td>16 (18%)</td>
</tr>
</tbody>
</table>

### Table 4  Number (%) of patients in whom carotid intima media thickness improved, stayed the same or got worse by group

<table>
<thead>
<tr>
<th>Group</th>
<th>Stayed the same*</th>
<th>Improved</th>
<th>Got worse</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>46 (48%)</td>
<td>6 (6%)</td>
<td>44 (46%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Placebo</td>
<td>26 (29%)</td>
<td>4 (4%)</td>
<td>61 (67%)</td>
<td></td>
</tr>
</tbody>
</table>

* Those with a change of <10% are defined as ‘stayed the same’.
† Based on a Pearson χ² test.

All patients with carotid plaque at baseline also had carotid plaque at follow-up. Among those without carotid plaque at baseline, there was no significant difference between the study groups with respect to the proportion with carotid plaque at follow-up (table 5).

### Changes in cardiovascular risk factors

Table 6 shows the changes observed in cardiovascular risk factors. Total cholesterol decreased in the atorvastatin group by 30.8 mg/dl (a reduction of 17%). The reduction in lipoprotein (a) was greater in the placebo group.

### Changes in markers of endothelial activation

There was no reduction in any marker of endothelial activation in the atorvastatin group compared with placebo (table 6).

### Disease activity

We compared SLE disease activity in the 2 years prior to randomisation with disease activity during the 2 years after randomisation to assess whether atorvastatin treatment had an impact on disease activity. There was an average of seven clinic visits per person prior to randomisation and seven after randomisation at which disease activity was measured. There was no significant change in mean disease activity after randomisation and no difference in the change in activity between the two treatment groups (table 7). In order to determine any beneficial effect of statins on renal function, we calculated the glomerular filtration rate using the Cockcroft–Gault equation. No statistical difference in renal function was seen between the two groups (p=0.34).

### Toxicity

Elevation in LFTs occurred throughout the trial as late as the 18-month visit. The proportion with abnormal alanine transaminase (ALT) levels during follow-up was 51% in the atorvastatin group compared with 31% in the placebo group (p=0.01). The proportion with a 50% increase in ALT during follow-up was 66% in the atorvastatin group and 44% in the placebo group (p=0.003). CK abnormalities did not differ between the groups. More patients in the atorvastatin group had thymic hyperplasia detected on CT scanning due to a disproportion at baseline. Seven had thymic hyperplasia at 24 months (but unchanged from baseline). There was no clinical myasthenia gravis. One patient had the acetylcholine receptor antibody at both baseline and 24 months.

### DISCUSSION

In spite of improved treatment of SLE, no improvement in cardiovascular mortality has been recognised in the last 25 years. Because statins help to reduce the risk of myocardial infarction even in patients with normal lipids, attributed to an anti-inflammatory effect (as demonstrated by reduction in hs-CRP), they seemed to be an ideal choice for intervention in the accelerated atherosclerosis of SLE.

Surprisingly, this 2-year intervention trial showed no benefit in the primary (coronary artery calcium) and secondary (carotid IMT, carotid plaque) atherosclerosis outcomes. Only in a post hoc analysis was there a suggestion of benefit for carotid IMT. In addition, there was no benefit in reduction of hs-CRP or any of the markers of endothelial activation, suggesting that atorvastatin has no anti-inflammatory effect in SLE that could be measured with these markers of inflammation.

Although statins may have some benefit for the disease activity of rheumatoid arthritis or multiple sclerosis, we found no evidence of a beneficial effect on SLE activity. Unlike most patients in whom liver enzyme elevation usually commences within the first 4 months of therapy, elevation of LFTs was common in this trial and occurred even late (18 months) in the trial. This suggests that patients with SLE receiving statins for hyperlipidaemia will require closer monitoring of LFTs.

In the general population, atorvastatin 80 mg prevents progression of coronary atherosclerosis, as measured by the percentage change in atheroma burden by intravascular ultrasound, and...
Table 6 Mean changes in cardiovascular risk factors and markers of endothelial activation

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD) at baseline</th>
<th>Mean (SD) at follow-up</th>
<th>Mean change</th>
<th>p Value comparing treatment groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP (µg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (n=96)</td>
<td>5.6 (8.5)</td>
<td>4.6 (5.9)</td>
<td>−1.0</td>
<td>0.62</td>
</tr>
<tr>
<td>Placebo (n=90)</td>
<td>6.3 (9.2)</td>
<td>4.5 (7.9)</td>
<td>−1.9</td>
<td></td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (n=96)</td>
<td>66.7 (67.2)</td>
<td>74.8 (70.7)</td>
<td>8.1</td>
<td>0.044</td>
</tr>
<tr>
<td>Placebo (n=90)</td>
<td>67.1 (75.9)</td>
<td>60.6 (69.0)</td>
<td>−6.6</td>
<td></td>
</tr>
<tr>
<td>Homocysteine (µM/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (n=96)</td>
<td>12.2 (4.1)</td>
<td>9.7 (3.4)</td>
<td>−2.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Placebo (n=90)</td>
<td>11.9 (3.6)</td>
<td>9.9 (3.5)</td>
<td>−2.0</td>
<td></td>
</tr>
<tr>
<td>ADMA (µM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atorvastatin (n=75)</td>
<td>0.33 (0.21)</td>
<td>0.27 (0.20)</td>
<td>−0.06</td>
<td>0.24</td>
</tr>
<tr>
<td>Placebo (n=70)</td>
<td>0.28 (0.20)</td>
<td>0.21 (0.19)</td>
<td>−0.07</td>
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<tr>
<td>Total cholesterol (mg/dl)</td>
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<td></td>
<td></td>
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<tr>
<td>Atorvastatin (n=99)</td>
<td>181.6 (38.1)</td>
<td>150.7 (40.7)</td>
<td>−30.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo (n=101)</td>
<td>190.1 (36.9)</td>
<td>195.6 (42.2)</td>
<td>5.5</td>
<td></td>
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<tr>
<td>Interleukin 6 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atorvastatin (n=95)</td>
<td>2.1 (3.0)</td>
<td>2.2 (3.0)</td>
<td>0.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Placebo (n=91)</td>
<td>2.4 (4.7)</td>
<td>1.9 (2.7)</td>
<td>−0.5</td>
<td></td>
</tr>
<tr>
<td>Soluble P-selectin (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atorvastatin (n=95)</td>
<td>108.7 (54.8)</td>
<td>99.7 (51.7)</td>
<td>−9.0</td>
<td>0.60</td>
</tr>
<tr>
<td>Placebo (n=91)</td>
<td>105.9 (56.0)</td>
<td>95.3 (47.6)</td>
<td>−10.6</td>
<td></td>
</tr>
<tr>
<td>Soluble intercellular adhesion molecule 1 (ng/ml)</td>
<td>435.7 (235.8)</td>
<td>471.8 (227.0)</td>
<td>36.2</td>
<td>0.44</td>
</tr>
<tr>
<td>Placebo (n=91)</td>
<td>385.8 (144.4)</td>
<td>454.5 (211.7)</td>
<td>68.7</td>
<td></td>
</tr>
<tr>
<td>Soluble vascular cell adhesion molecule 1 (ng/ml)</td>
<td>1066.5 (632.2)</td>
<td>1113.1 (617.5)</td>
<td>46.6</td>
<td>0.63</td>
</tr>
<tr>
<td>Placebo (n=91)</td>
<td>1046.0 (613.9)</td>
<td>1133.7 (630.7)</td>
<td>87.7</td>
<td></td>
</tr>
</tbody>
</table>

*Based on an ANCOVA model controlling for baseline level. ADMA, asymmetric dimethyl arginine.

Table 7 Mean systemic lupus erythematosus disease activity index (SLEDAI) by group and period

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (range) SLEDAI before randomisation</th>
<th>Mean (range) SLEDAI after randomisation</th>
<th>Change</th>
<th>p Value for change</th>
<th>Difference in change between groups</th>
<th>p Value for difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLEDAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>2.0 (0–18)</td>
<td>2.2 (0–24)</td>
<td>0.2</td>
<td>0.45*</td>
<td>0.1</td>
<td>0.92*</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.9 (0–14)</td>
<td>2.0 (0–18)</td>
<td>0.1</td>
<td>0.54*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>0.63 (0–3)</td>
<td>0.72 (0–3)</td>
<td>0.09</td>
<td>0.034*</td>
<td>0.09</td>
<td>0.19*</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.68 (0–3)</td>
<td>0.67 (0–3)</td>
<td>0.00</td>
<td>0.81*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on a mixed-effects model to account for repeated measures of SLEDAI on the same patients. PGA, Physician Global Assessment.

Acknowledgements The Data Safety Monitoring Board consisted of John Klippel (rheumatologist), Joan Von Feldt (rheumatologist and chairperson), Mark Gourley (safety officer), William F Rosenberg (statistician), Lenore Buckley (rheumatologist), Matthew Liang (rheumatologist), Gary Gerstenblith (cardiologist) and Joseph E Craft (rheumatologist). Pfizer Pharmaceuticals donated atorvastatin and matching placebo.

Funding The Lupus Atherosclerosis Prevention Study was supported by a grant from the Alliance for Lupus Research, the Arthritis Foundation, the Hopkins Lupus Cohort (NIH AR 43727) and by grant number UL1 RR 025005 from the National Center for Research Resources (NCRR).

Competing interests MAP was formerly on a Pfizer Advisory Board and a Pfizer Speakers Bureau unrelated to atorvastatin. None of the other authors had any other competing interests.

Ethics approval This study was conducted with the approval of the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

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*Ann Rheum Dis* 2011 70: 760-765 originally published online December 21, 2010
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