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## Secondary analysis of APPLE study suggests atorvastatin may reduce atherosclerosis progression in pubertal lupus patients with higher C reactive protein

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SLB sadly died before the publication of this article.

**Collaborator** NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents.

**Contributors** SPA, LES, CIS, HXB, GWE and EY formed the hypothesis and SPA, HXB, EY and GE performed the analysis. SPA, LES, CIS, HXB, GWE and DL interpreted the results. All authors contributed to writing, editing and reviewing the manuscript and approved the final version of the paper. All authors had access to the data. And can take responsibility for the integrity of the data and accuracy of the data analysis.

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## Abstract

**Objective**—Participants in the Atherosclerosis Prevention in Paediatric Lupus Erythematosus (APPLE) trial were randomised to placebo or atorvastatin for 36 months. The primary endpoint, reduced carotid intima medial thickness (CIMT) progression, was not met but atorvastatin-treated participants showed a trend of slower CIMT progression. Post-hoc analyses were performed to assess subgroup benefit from atorvastatin therapy.

**Methods**—Subgroups were prespecified and defined by age (> or < 15.5 years), systemic lupus erythematosus (SLE) duration (> or < 24 months), pubertal status (Tanner score ≥ 4 as post-pubertal or < 4 as pre-pubertal), low density lipoprotein cholesterol (LDL) (> or < 110 mg/dl) and high-sensitivity C reactive protein (hsCRP) (> or < 1.5 mg/l). A combined subgroup (post-pubertal and hsCRP > 1.5 mg/l) was compared to all others. Longitudinal linear mixed-effects models were developed using 12 CIMT and other secondary APPLE outcomes (lipids, hsCRP, disease activity and damage, and quality of life). Three way interaction effects were assessed for models.

**Results**—Significant interaction effects with trends of less CIMT progression in atorvastatin-treated participants were observed in pubertal (3 CIMT segments), high hsCRP (2 CIMT segments), and the combined high hsCRP and pubertal group (5 CIMT segments). No significant treatment effect trends were observed across subgroups defined by age, SLE duration, LDL for CIMT or other outcome measures.

**Conclusions**—Pubertal status and higher hsCRP were linked to lower CIMT progression in atorvastatin-treated subjects, with most consistent decreases in CIMT progression in the combined pubertal and high hsCRP group. While secondary analyses must be interpreted cautiously, results suggest further research is needed to determine whether pubertal lupus patients with high CRP benefit from statin therapy.

**ClinicalTrials.gov identifier**—NCT00065806.

Over the past 50 years, improvements in systemic lupus erythematosus (SLE) diagnosis and management have substantially reduced morbidity and mortality from acute disease.<sup>12</sup> With longer-term survival, accelerated atherosclerosis has emerged as an important long-term complication of SLE.<sup>34</sup> Traditional cardiovascular risk factors do not account for the premature atherosclerosis characteristic of SLE<sup>25</sup>; therefore, understanding atherosclerosis mechanisms and identifying effective prevention strategies in this high risk population remain areas of intense research.

Because 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, or statins, are effective in primary and secondary atherosclerosis prevention in the adult general population<sup>67</sup> and have pleiotropic immunomodulatory effects,<sup>8</sup> statins have been proposed to treat patients with SLE. Three recent randomised, placebo controlled clinical trials have investigated the efficacy and safety of statins in prevention of SLE-related atherosclerosis.<sup>9–11</sup>

The Lupus Atherosclerosis Prevention Study (LAPS) randomised 200 adult SLE participants (aged 18–78 years) to 24 months of placebo or atorvastatin therapy (40 mg/day). There were no statistically significant differences between treatment groups in the primary endpoint, CT coronary calcium score. In addition, changes in carotid intima medial thickness (CIMT) were not significantly different between treatment groups; however, post-hoc analysis suggested that fewer patients in the atorvastatin group showed CIMT progression.<sup>9</sup>

The Atherosclerosis Prevention in Paediatric Lupus Erythematosus (APPLE) study randomised 221 patients with SLE (aged 10–21 years) to 36 months of atorvastatin (10–20 mg/day, based on weight) versus placebo treatment. Results showed no statistically significant difference in CIMT progression between treatment and placebo groups; however there was a trend towards reduced CIMT progression in the atorvastatin treated group in other measured CIMT segments.<sup>10</sup>

In a randomised, placebo controlled trial of 60 adult SLE patients randomised to atorvastatin (40 mg/day) or placebo for 1 year, the overall plaque volume and coronary calcium score on multi-detector CT increased in the placebo group but not in the atorvastatin group.<sup>11</sup>

Even though the APPLE and LAPS trials failed to meet their primary endpoints, trends observed in both studies suggested atorvastatin may reduce CIMT progression in a subset of patients. Consequently, we performed post-hoc analyses of the APPLE cohort to assess treatment effects across pre-specified subgroups defined by variables linked to cardiovascular risk and CIMT—low density lipoprotein cholesterol (LDL), high-sensitivity C reactive protein (hsCRP), age—as well as duration of lupus and pubertal status. We

hypothesised that participants with higher baseline LDL, higher hsCRP, older age, longer duration of lupus, and post-pubertal status would show decreased CIMT progression on statin therapy.

The subgroups were defined prior to performing secondary analyses. Because atherogenic foam cells begin to accumulate at puberty<sup>1213</sup> and the impact of puberty was not assessed in the primary APPLE study,<sup>10</sup> pubertal status was of particular interest for post-hoc analyses. In assessing the impact of pubertal status, age was considered as a potential confounder. Lipid status and hsCRP were included in these analyses as predictors of cardiovascular mortality which are influenced by statin therapy.<sup>614</sup> Given the need to limit the number of comparisons performed, other potentially important variables including SLE disease activity, presence of nephritis, history of hypertension, body mass index, antiphospholipid antibody positivity and cumulative steroid usage were not included. Thus, the objective of these subgroup analyses was to determine whether or not baseline cardiovascular risk factors (LDL and hsCRP), age, pubertal status and duration of SLE influenced response to statin therapy in the APPLE cohort.

## PATIENTS AND METHODS

### APPLE design

The design and methods of the APPLE trial have been reported previously.<sup>15</sup> Briefly, APPLE is a multicentre prospective, randomised, placebo controlled trial, enrolling 221 participants (84% female, mean age 15.7 years) with SLE defined by American College of Rheumatology criteria<sup>16</sup> from 21 North American centres. Patients were excluded if they had baseline fasting total cholesterol >350 mg/dl, familial hypercholesterolaemia, nephrotic syndrome, renal insufficiency, liver disease or were pregnant or nursing. Subjects were randomised to receive daily atorvastatin (>50 kg: 10 mg/day, increasing to 20 mg/day at day 30; 50 kg: 10 mg/day) with background usual medical treatment for SLE at the discretion of the treating paediatric rheumatologist. Hydroxychloroquine, low-dose aspirin, multivitamins containing folate (400 µg), and American Heart Association Therapeutic Lifestyle Changes diet were recommended.

### B-mode ultrasonography of carotid arteries

Seven CIMT examinations were performed over the course of the study, with two at enrolment and two at study end. Additional CIMT measurements were scheduled at 6, 12 and 24 months. Standardised measurements of CIMT were obtained using an ultrasound protocol described in detail previously.<sup>10</sup> Standardised longitudinal b-mode images were collected for three bilateral arterial segments defined relative to the tip of the flow divider (TFD) as the common carotid artery (CCA) (from 10 to 20 mm proximal to the TFD), the carotid bifurcation (from the TFD to 10 mm proximal to the TFD) and the proximal 10 mm of the internal carotid artery (ICA) providing a set of 12 CIMT measurement sites. All ultrasound scans were read by a single experienced reader using Image Pro software (Media Cybernetics, Bethesda, Maryland, USA). For each segment, both near and far walls were measured, and maximum and mean CIMT measurements recorded. The Ward R. Riley Ultrasound Center supervised quality assurance procedures, including central training and

certification of all sonographers and the reader as well as regular site visits and performance reviews.

For each measurement site, a maximum CIMT value defined as the largest of the four angle-specific maximum CIMTs was calculated. These 12 maximum CIMT values were then averaged to determine the mean–max CIMT over near and far walls of the right and left CCA, carotid bifurcation and ICA. For each of the four measurement sites in the CCA, a mean CIMT value defined as the average of the four angle-specific mean CIMTs was also calculated. The four mean CIMT values were then averaged to determine the mean–mean common CIMT. Other CIMT outcomes, including an overall mean–mean and other segment/wall-specific mean–max or mean–mean CIMT measures were computed accordingly.

Other assessments including fasting lipid levels, modified Safety of Oestrogens in Lupus Erythematosus: National Assessment version of the SLE Disease Activity Index (SELENA SLEDAI),<sup>17</sup> Systemic Lupus International Collaborating Clinics/ACR Damage Index,<sup>18</sup> and PedsQL 4.0<sup>19</sup> and PedsQL Rheumatology module 3.0<sup>20</sup> were obtained as previously reported.<sup>1521</sup>

### Definition of subgroups

All subgroups were determined prior to performing secondary analyses. Subgroups were defined by five variables as follows.<sup>22</sup> Participants  $\geq 15.5$  years of age were compared to younger participants. The selected age threshold represents the mean age of the APPLE cohort. Participants with SLE duration  $\geq 24$  months were compared to those with more recently diagnosed disease. Pubertal status was assessed using a validated, patient reported measure.<sup>23</sup> Participants were given a standardised series of drawings with explanatory text to assess pubertal development. Girls were given line drawings of the five stages of breast and female pubic hair development with appropriate written descriptions accompanying the drawings. Boys were given line drawings of boys showing the five stages of pubic hair development with appropriate written descriptions. Each participant was asked to select the drawing best representing his or her own development.<sup>23</sup> Prepubertal status was defined as Tanner stage  $<4$  in breast (for female) or genital (for male). Participants with a baseline LDL  $<110$  mg/dl were compared to those  $\geq 110$  mg/dl. This LDL cut point was chosen based on National Cholesterol Education Program recommendations for children and adolescents.<sup>24</sup> Those with hsCRP  $<1.5$  mg/l were compared to those  $\geq 1.5$  mg/l. The hsCRP cut point represents the 75th percentile for healthy US females aged 16–19 years<sup>25</sup> and falls within the ‘average risk’ range for the general adult population (1.0–3.0 mg/l) defined by the American Heart Association.

After reviewing the results for the five predefined subgroup variables, we then defined an additional subgroup based on the combination of post-pubertal status plus elevated baseline hsCRP ( $\geq 1.5$  mg/l) versus all others.

### Outcome measures

The primary and secondary longitudinal CIMT outcomes from the APPLE trial were used as outcomes for the subgroup analyses. These included the mean–mean common CIMT

(primary outcome measure of the APPLE trial), the mean–max CIMT of 12 segments and the mean–max and mean–mean CIMT of each of the 12 individual carotid artery segments, lipid outcomes, hsCRP, total cholesterol, high density lipoprotein cholesterol (HDL), LDL, triglycerides, lipoprotein A and homocysteine as well as disease outcomes and quality of life measures. In addition, differences in treatment effect within the subgroups were analysed for hsCRP, levels of total cholesterol, HDL, LDL, triglycerides, lipoprotein A and homocysteine as well as disease outcomes and quality of life measures. Based on preliminary analyses suggesting effects of pubertal status and hsCRP on CIMT only, the combined puberty and hsCRP subgroup was analysed for treatment effect on CIMT progression and not other outcomes.

### Statistical analysis

Baseline characteristics were summarised using descriptive statistics with categorical data presented as percentages and continuous data presented as means, SDs and medians. Baseline characteristics between subgroups were compared using the  $\chi^2$  test, Fisher's exact test, or the non-parametric Wilcoxon test. The primary efficacy analysis for APPLE compared rates of mean–mean common CIMT progression between treatment groups based on a test of two-way interaction between treatment group and time in a longitudinal linear mixed effects model under data missing at random assumptions.<sup>10</sup> From this model, the effect of treatment can be estimated as the difference in mean progression rates between participants assigned to atorvastatin and placebo treatment groups, with negative differences indicating progression for the atorvastatin group was slower than for the placebo group. Similar models were used to assess other CIMT and non-CIMT outcomes.

To examine heterogeneity of treatment effects across subgroups, the efficacy model used in the primary APPLE analysis was extended to include an indicator variable for subgroup as well as two- and three-way interactions between subgroup, treatment group and time. From these models, we provide estimated mean progression rates with 95% CIs for each combination of subgroup and treatment group. Finally, the three-way interaction between subgroup, treatment group and time provides a test of whether treatment effects in terms of progression rate differ significantly between subgroups. Initially, models were fit examining one subgroup variable at a time.

All statistical analyses were two-sided with the level of significance set at 0.05. With five subgroup variables, 12 different CIMT outcomes and 11 other outcomes plus the combined subgroup and 12 different CIMT outcomes, we performed a total of 127 tests of three-way interactions in these exploratory analyses. If all of these tests were independent, we would expect approximately six tests to achieve statistical significance due to chance alone. These results should be interpreted cautiously as hypothesis generating and not hypothesis testing. Analyses were performed with SAS V.9.2.

## RESULTS

Baseline characteristics of the subgroups are summarised in tables 1 and 2.



### Pubertal subgroups results

For the subgroups defined by pre- and post-pubertal status, the treatment effects on CIMT progression are summarised in table 3. In the post-pubertal subgroup, atorvastatin-treated patients showed less CIMT progression in the mean–mean bifurcation ( $p=0.004$ ; model interaction effect  $p=0.019$ ), mean–max near wall ( $p=0.039$ , model interaction effect  $p=0.027$ ) and mean–mean near wall ( $p=0.058$ , model interaction effect  $p=0.021$ ). In addition, the pre-pubertal atorvastatin group had larger increases in PedsQL ( $p=0.011$ ; model interaction effect  $p=0.014$ ) and rheumatology PedsQL child/teen scores ( $p=0.002$ , model interaction effect  $p=0.002$ ) compared to the placebo treated group. There were no differences in the pubertal patients nor in either group for the parent PedsQL scores. The post-pubertal atorvastatin-treated group experienced a reduction in HDL compared to the placebo group ( $p=0.014$ ; interaction effect  $p=0.013$ ). No significant trends in treatment effect differences were seen between subgroups for other outcome measures.

### Age subgroups results

For the subgroups defined by age, there were no significant differences in treatment effect on CIMT progression or other outcome measures.

### SLE duration subgroups results

For the subgroups defined by duration of SLE, the atorvastatin-treated group with <24 months' duration SLE had greater increase in child/teen rheumatology specific QL scores only. There were no other significant differences in treatment effect on CIMT progression or other outcome measures.

### HsCRP subgroups results

For subgroups defined by baseline hsCRP level, the treatment effects on CIMT outcomes are summarised in table 4. For the high hsCRP cohort, CIMT progression rates were lower in the atorvastatin treatment group for two CIMT segments, mean–mean common ( $p=0.029$ , model interaction effect  $p=0.049$ ) and mean–mean near wall ( $p=0.014$ ; model interaction effect  $p=0.014$ ). In addition, in the high hsCRP, atorvastatin group, child/teen PedsQL scores increased more than in the placebo group. For the low hsCRP group, there were no differences in rheumatology specific or parent PedsQL scores. No significant trends in treatment effect differences were seen for other outcome measures.

### LDL subgroups results

For subgroups defined by baseline LDL level, models showed no difference in treatment effects on CIMT progression, and levels of HDL, hsCRP and homocysteine. As expected, reductions in LDL ( $p=0.001$ ; model interaction effect  $p=0.013$ ) and total cholesterol ( $p<0.001$ , model interaction effect  $p=0.008$ ) were greater in the atorvastatin treatment group compared to placebo for both high and low LDL subgroups. More substantial reductions in triglyceride ( $p=0.015$ , model interaction effect  $p=0.032$ ) and lipoprotein A levels ( $p=0.003$ , model interaction effect  $p=0.007$ ), were observed in the atorvastatin-treated subjects with baseline LDL 110 mg/dl.



**Combined puberty and hsCRP subgroups results**—For the subgroups defined by those who were pubertal with high hsCRP versus all others, the treatment effects on CIMT progression are summarised in table 5. In the subgroup of pubertal subjects with high hsCRP, the atorvastatin-treated group had lower rates of CIMT progression in five of 12 CIMT outcomes: mean–mean common ( $p=0.004$ , model interaction effect  $p=0.005$ ), mean–mean ( $p=0.001$ ; model interaction effect  $p=0.008$ ), mean–mean bifurcation ( $p=0.002$ ; model interaction effect  $p=0.023$ ), mean–max near wall ( $p=0.003$ , model interaction effect  $p=0.029$ ) and mean–mean near wall ( $p<0.001$ , model interaction effect  $p=0.002$ ).

## DISCUSSION

APPLE is the largest randomised, double blind placebo controlled trial in paediatric lupus and the only clinical trial to examine efficacy of safety of statin use in children and adolescents with SLE. Importantly, the APPLE trial demonstrated that CIMT progressed in the placebo group in all but one CIMT segment and at a faster rate than expected in the general paediatric population.<sup>10</sup> Thus, the premature atherosclerosis of SLE is present even in children and adolescents, highlighting the need to identify particularly high risk individuals who may benefit from aggressive prevention strategies. Although the APPLE trial did not show significant benefit of atorvastatin treatment in the primary endpoint, a signal of reduced CIMT progression in the atorvastatin group was evident across multiple CIMT segments, raising the question of whether subgroups of the study population may have benefited from statin therapy.<sup>10</sup> The current post hoc secondary analyses were performed in order to identify high risk subgroups that may benefit from statin therapy with clinically significant reduction in CIMT progression.

Trends towards reduced CIMT progression were observed in the atorvastatin-treated high hsCRP (two CIMT segments) and in the post-pubertal subgroups (three CIMT segments). Interestingly, the effect of puberty was not mediated by age alone. In fact, the age subgroup analysis ( 15.5 vs 15.5 years), showed no differences in CIMT progression between the atorvastatin and placebo treatment groups. Based on these observations, a high-risk subgroup was then defined made up of post-pubertal participants who had an elevated hsCRP at baseline. The most consistent observations of treatment effect on CIMT were observed in this combined post-pubertal and high hsCRP subgroup. CIMT progression was slower in the atorvastatin group across five CIMT segments, with an observed magnitude of mean difference in CIMT progression of  $>0.0045$  mm/year between the atorvastatin and placebo treatment groups for these segments. This magnitude of difference in CIMT progression between the two groups satisfies the threshold for clinically significant CIMT change as originally defined in the APPLE trial.<sup>10</sup> Informing this definition of clinically significant change in CIMT for the APPLE trial were large epidemiological studies in adults which demonstrated a 41–47% increase in risk of cardiovascular events for every 0.16–0.20 mm increase in CIMT.<sup>26–29</sup> Therefore, for a 15-year-old with SLE, a decrease in CIMT progression rate of at least 0.0045 mm/y for over 35 years ( $0.0045$  mm/year $\times$ 35 years=0.16 mm) could achieve 40% reduction of risk by age 50.

These analyses suggest that post-pubertal adolescents with SLE who have hsCRP 1.5 mg/l may benefit from atorvastatin therapy. This group may be at particularly high risk for SLE-

related premature atherosclerosis and more responsive to statin therapy for several reasons. CIMT remains stable during childhood and begins to increase during adolescence<sup>3031</sup>; however, no published studies address how pubertal status physiologically influences progression of subclinical atherosclerosis in SLE. In a longitudinal study of CIMT in children and adolescents with type I diabetes mellitus, those with more advanced pubertal status achieved a higher mean increase in CIMT z-scores over 2 years of follow-up.<sup>32</sup> In randomised, controlled trials assessing statin efficacy in paediatric familial hypercholesterolaemia trials, statins were effective in reducing CIMT across all ages (8–18 years) and pubertal subgroup analyses were not performed.<sup>3334</sup> Pubertal development likely influences the susceptibility and severity of SLE, particularly in females. SLE is most common in females during their reproductive years,<sup>35</sup> and post-menopausal women with SLE who take hormone replacement therapy are at higher risk of disease flare,<sup>17</sup> suggesting that oestrogen exposure is an important mediator of disease expression. It is possible that pubertal patients with elevated hsCRP comprise a ‘perfect storm’ in which the presence of chronic inflammation in the hormonal milieu of puberty creates a proatherogenic environment in which CIMT progression is accelerated. Statins may abrogate this process.

Statins are currently recommended for primary prevention of atherosclerosis in adults with elevated LDL, and momentum is growing for use in adults with isolated high hsCRP. The landmark Justification for Use of Statins in Primary Prevention: An Intervention Evaluating Rosuvastatin (JUPITER) trial randomised 17 000 adults without cardiovascular disease who had normal LDL but high hsCRP (>2.0 mg/dl) to rosuvastatin or placebo.<sup>14</sup> The rosuvastatin treatment group had lower rates of myocardial infarction, stroke and death, prompting early discontinuation of the trial. On the other hand, the Heart Protection Study randomised more than 20 000 adults without cardiovascular disease to simvastatin or placebo, stratifying them by hsCRP levels.<sup>36</sup> The risk of developing cardiovascular events after 5 years of treatment was reduced in the statin group but did not differ according to hsCRP status. Use of statins as primary prevention has not been explored in the general paediatric population but is effective in preventing CIMT progression in children with familial hypercholesterolaemia. In the population-based Bogalusa Heart Study, hsCRP levels did not predict CIMT progression in healthy young adults over a relatively short follow-up period (2.4 years).<sup>37</sup> It is important to note that results from healthy cohorts and adults are difficult to extrapolate to adolescent and young adult lupus patients who have a unique cardiovascular risk profile. Taken together, the results of these analyses do not provide a mandate for use of statins for primary prevention in pubertal adolescents and young adults with SLE who have elevated hsCRP, but suggest that this group may benefit from statin therapy and, according to APPLE trial safety data, are unlikely to experience harm.

The impact of statins on CIMT progression varied across the 12 different carotid segments that were studied. Likewise, CIMT progression in the placebo group was not uniform across all segments. Segment-specific risk factor associations have been reported previously in adult and paediatric CIMT studies and are thought to reflect the influence on focal thickening of local phenomena such as shear stress and arterial remodelling, but the clinical significance is unknown.<sup>38–40</sup> While intriguing, these exploratory analyses have several limitations. Post-hoc subgroup analyses are inherently limited and often underpowered due to the small size of subgroups studied. Multiple statistical comparisons were performed,

increasing the probability that some of the observed statistically significant findings were due to chance. Interaction effects to test for differences between treatment groups were used to reduce the risk of chance observations. Although chance findings may result in a significant result among subgroups where no treatment effect was seen in the overall cohort (eg, in the quality of life differences observed in these analyses), the combined puberty and elevated hsCRP subgroup demonstrated a treatment effect across multiple CIMT segments and similar in direction to the overall APPLE cohort. Prospective, controlled studies are needed to confirm these findings.

In summary, pubertal status and higher hsCRP were linked to lower rates of CIMT progression in atorvastatin-treated subjects in post-hoc subgroup analyses of the APPLE trial data. The most consistent reduction in CIMT progression was observed among the pubertal subgroup which also had a high baseline hsCRP. These findings suggest that the ‘one size fits all’ approach towards cardiovascular prevention in SLE should be re-examined to include identification of specific high risk subgroups that may benefit from more aggressive primary prevention interventions, including statin therapy.

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**Table 1**

Baseline characteristics by age, duration of lupus and pubertal status

| Variable                                 | Age             |                 |                 | Duration of lupus |                |                 | Pubertal status |  |
|--|-----------------|-----------------|-----------------|-------------------|----------------|-----------------|-----------------|--|
|  | <15.5 years     | 15.5 years      | <24 months      | 24 months         | Pre-pubertal   | Post-pubertal   |                 |  |
| Female sex, no. (%)                      | 91/110 (82.7%)  | 93/111 (83.8%)  | 90/106 (84.9%)  | 94/115 (81.7%)    | 61/72 (84.7%)  | 123/148 (83.1%) |                 |  |
| Age (year), mean (SD)                    | 13.6 (1.5)*     | 17.9 (1.6)*     | 14.9 (2.3)*     | 16.5 (2.7)*       | 13.7 (2.1)*    | 16.7 (2.3)*     |                 |  |
| White race, no. (%)                      | 49/110 (44.5%)* | 65/111 (58.6%)* | 59/106 (55.7%)  | 55/115 (47.8%)    | 29/72 (40.3%)* | 84/148 (56.8%)* |                 |  |
| Hispanic or Latino, no. (%)              | 27/110 (24.5%)  | 27/111 (24.3%)  | 27/106 (25.5%)  | 27/115 (23.5%)    | 16/72 (22.2%)  | 38/148 (25.7%)  |                 |  |
| BMI (kg/m <sup>2</sup> ), mean (SD)      | 23.5 (5.3)*     | 25.3 (5.3)*     | 24.4 (5.2)      | 24.4 (5.5)        | 23.1 (5.4)*    | 25.1 (5.2)*     |                 |  |
| Duration SLE (months), mean (SD)         | 22.6 (21.3)*    | 39.3 (32.1)*    | 9.0 (6.4)*      | 51.2 (25.8)*      | 26.6 (30.6)*   | 33.3 (27.3)*    |                 |  |
| SDI=0, no. (%)                           | 88/110 (80.0%)* | 74/111 (66.7%)* | 87/106 (82.1%)* | 75/115 (65.2%)*   | 54/72 (75.0%)  | 107/148 (72.3%) |                 |  |
| SLEDAI, mean (SD)                        | 4.7 (4.3)       | 4.8 (4.2)       | 5.1 (4.4)       | 4.4 (4.2)         | 5.0 (4.8)      | 4.6 (4.0)       |                 |  |
| Hx hypertension, no. (%)                 | 36/107 (33.6%)  | 37/107 (34.6%)  | 31/101 (30.7%)  | 42/113 (37.2%)    | 21/72 (29.2%)  | 52/141 (36.9%)  |                 |  |
| Hx nephritis/nephrotic syndrome, no. (%) | 46/109 (42.2%)  | 45/111 (40.5%)  | 35/105 (33.3%)* | 56/115 (48.7%)*   | 26/72 (36.1%)  | 53/147 (36.1%)  |                 |  |
| Proteinuria, no. (%)                     | 27/110 (24.5%)  | 29/110 (26.4%)  | 24/106 (22.6%)  | 32/114 (28.1%)    | 31/72 (43.1%)  | 60/147 (40.8%)  |                 |  |
| C3 (mg/dl), mean (SD)                    | 102.2 (27.7)    | 99.3 (30.2)     | 100.3 (26.9)    | 101.1 (30.9)      | 16/72 (22.2%)  | 40/147 (27.2%)  |                 |  |
| C4 (mg/dl), mean (SD)                    | 15.5 (11.0)     | 15.6 (8.2)      | 14.7 (7.7)      | 16.4 (11.1)       | 102.4 (27.3)   | 99.9 (29.9)     |                 |  |
| Prednisone dose (mg/kg), mean (SD)       | 0.2 (0.2)       | 0.2 (0.2)       | 0.2 (0.2)*      | 0.1 (0.2)*        | 14.7 (7.7)     | 15.9 (10.5)     |                 |  |
| Immunosuppressant, <sup>†</sup> no. (%)  | 41/107 (38.3%)  | 43/106 (40.6%)  | 38/101 (37.6%)  | 46/112 (41.1%)    | 0.2 (0.2)      | 0.2 (0.2)       |                 |  |
| hsCRP (mg/l), mean (SD)                  | 2.7 (8.5)       | 4.3 (17.6)      | 2.4 (8.1)*      | 4.7 (17.7)*       | 30/69 (43.5%)  | 54/144 (37.5%)  |                 |  |
| Log hsCRP, mean (SD)                     | -0.28 (1.44)    | -0.29 (1.61)    | -0.57 (1.48)*   | -0.02 (1.52)*     | 3.2 (7.8)      | 3.8 (16.2)      |                 |  |
| Homocysteine (μmol/l), mean (SD)         | 7.2 (3.0)       | 7.7 (3.2)       | 7.8 (3.3)       | 7.2 (2.8)         | -0.10 (1.53)   | -0.37 (1.52)    |                 |  |
| Total cholesterol (mg/dl), mean (SD)     | 154.7 (36.4)    | 155.6 (39.7)    | 157.4 (40.8)    | 153.0 (35.0)      | 7.4 (3.5)      | 7.5 (2.9)       |                 |  |
| HDL (mg/dl), mean (SD)                   | 46.4 (11.7)     | 46.2 (13.8)     | 46.1 (12.3)     | 46.5 (13.2)       | 154.6 (35.6)   | 155.4 (39.3)    |                 |  |
| LDL (mg/dl), mean (SD)                   | 85.7 (31.3)     | 87.0 (31.6)     | 86.9 (34.1)     | 85.8 (28.7)       | 45.5 (12.3)    | 46.7 (13.1)     |                 |  |
| Triglycerides (mg/dl), mean (SD)         | 116.0 (71.9)    | 112.0 (60.7)    | 125.2 (78.0)*   | 103.5 (51.2)*     | 85.6 (31.6)    | 86.8 (31.5)     |                 |  |
| Lipoprotein A (mg/dl), mean (SD)         | 21.4 (26.0)     | 24.8 (27.6)     | 22.7 (27.6)     | 23.6 (26.2)       | 117.4 (53.3)   | 112.1 (72.3)    |                 |  |
| Mean–mean common IMT (mm), mean (SD)     | 0.468 (0.043)   | 0.468 (0.042)   | 0.464 (0.045)   | 0.472 (0.040)     | 20.4 (24.2)    | 24.6 (28.0)     |                 |  |
| Mean–max IMT (mm), mean (SD)             | 0.574 (0.052)*  | 0.592 (0.058)*  | 0.572 (0.058)*  | 0.593 (0.053)*    | 0.466 (0.045)  | 0.469 (0.041)   |                 |  |



| Variable                         | Age           |               | Duration of lupus |               | Pubertal status |               |
|----------------------------------|---------------|---------------|-------------------|---------------|-----------------|---------------|
|                                  | <15.5 years   | 15.5 years    | <24 months        | 24 months     | Pre-pubertal    | Post-pubertal |
| Mean-maximal IMT (mm), mean (SD) | 0.582 (0.058) | 0.587 (0.051) | 0.574 (0.060)     | 0.587 (0.054) | 0.574 (0.060)   | 0.587 (0.054) |

\* p<0.05 for the comparison between subgroup treatment arms.

† Current use of methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide or rituximab.

BMI, body mass index; HDL, high density lipoprotein cholesterol; hsCRP, high sensitivity C reactive protein; Hx, history of; IMT, intima medial thickening; LDL, low density lipoprotein cholesterol; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.



Table 2

Baseline characteristics by CRP, LDL and CRP/pubertal status

| Variable                                 | hsCRP           |               | LDL             |                | hsCRP/pubertal status         |                        |
|--|-----------------|---------------|-----------------|----------------|-------------------------------|------------------------|
|  | <1.5 mg/l       | 1.5 mg/l      | <110 (mg/dl)    | 110 (mg/dl)    | Not ( 1.5 mg/l post-pubertal) | 1.5 mg/l post-pubertal |
| Female sex, no. (%)                      | 119/144 (82.6%) | 47/59 (79.7%) | 134/163 (82.2%) | 39/47 (83.0%)  | 157/189 (83.1%)               | 27/32 (84.4%)          |
| Age (year), mean (SD)                    | 15.7 (2.7)      | 15.9 (2.6)    | 15.7 (2.8)      | 15.6 (2.3)     | 15.5 (2.6)*                   | 17.3 (2.4)*            |
| White race, no. (%)                      | 78/144 (54.2%)  | 27/59 (45.8%) | 94/163 (57.7%)* | 17/47 (36.2%)* | 96/189 (50.8%)                | 18/32 (56.3%)          |
| Hispanic or Latino, no. (%)              | 37/144 (25.7%)  | 17/59 (28.8%) | 41/163 (25.2%)  | 13/47 (27.7%)  | 42/189 (22.2%)                | 12/32 (37.5%)          |
| BMI (kg/m <sup>2</sup> ), mean (SD)      | 23.6 (4.4)      | 25.7 (6.3)    | 24.1 (5.2)      | 24.7 (5.2)     | 24.1 (5.2)                    | 26.5 (5.6)             |
| Duration SLE (months), mean (SD)         | 28.3 (26.8)     | 35.8 (30.5)   | 29.8 (27.7)     | 31.4 (28.1)    | 30.2 (29.4)                   | 35.4 (22.1)            |
| SLEI=0, no. (%)                          | 107/144 (74.3%) | 40/59 (67.8%) | 121/163 (74.2%) | 33/47 (70.2%)  | 142/189 (75.1%)               | 20/32 (62.5%)          |
| SLEDAI, mean (SD)                        | 4.7 (4.0)       | 5.0 (4.9)     | 4.1 (3.5)*      | 6.9 (5.5)*     | 4.7 (4.2)                     | 4.9 (4.5)              |
| Hx hypertension, no. (%)                 | 47/139 (33.8%)  | 18/58 (31.0%) | 44/157 (28.0%)* | 21/47 (44.7%)* | 62/183 (33.9%)                | 11/31 (35.5%)          |
| Hx nephritis/nephrotic syndrome, no. (%) | 52/143 (36.4%)  | 20/59 (33.9%) | 59/162 (36.4%)* | 26/47 (55.3%)* | 68/188 (36.2%)                | 11/32 (34.4%)          |
| Proteinuria, no. (%)                     | 60/143 (42.0%)  | 24/59 (40.7%) | 30/163 (18.4%)* | 22/46 (47.8%)* | 78/188 (41.5%)                | 13/32 (40.6%)          |
| C3 (mg/dl), mean (SD)                    | 34/143 (23.8%)  | 18/59 (30.5%) | 101.8 (25.8)    | 96.6 (38.4)    | 49/188 (26.1%)                | 7/32 (21.9%)           |
| C4 (mg/dl), mean (SD)                    | 98.7 (27.3)     | 105.6 (33.1)  | 15.3 (7.1)      | 16.4 (15.8)    | 99.7 (28.6)                   | 106.4 (31.2)           |
| Prednisone dose (mg/kg), mean (SD)       | 15.5 (10.4)     | 16.1 (7.9)    | 0.2 (0.2)*      | 0.3 (0.2)*     | 15.5 (10.0)                   | 16.0 (7.5)             |
| Immunosuppressant, <sup>†</sup> no. (%)  | 0.2 (0.2)       | 0.2 (0.2)     | 58/158 (36.7%)  | 23/45 (51.1%)  | 0.2 (0.2)                     | 0.1 (0.1)              |
| hsCRP (mg/l), mean (SD)                  | 54/140 (38.6%)  | 25/56 (44.6%) | 4.2 (15.7)      | 1.4 (1.9)      | 71/182 (39.0%)                | 13/31 (41.9%)          |
| Log hsCRP, mean (SD)                     | 0.5 (0.4)*      | 11.0 (24.4)*  | -0.25 (1.59)    | -0.39 (1.28)   | 1.5 (5.0)*                    | 14.3 (31.3)*           |
| Homocysteine (μmol/l), mean (SD)         | -1.04 (0.92)*   | 1.55 (1.07)*  | 7.4 (3.1)       | 7.9 (2.9)      | -0.66 (1.27)*                 | 1.72 (1.16)*           |
| Total cholesterol (mg/dl), mean (SD)     | 7.3 (2.8)       | 7.9 (3.6)     | 140.0 (22.7)*   | 207.4 (33.9)*  | 7.5 (3.1)                     | 7.4 (2.7)              |
| HDL (mg/dl), mean (SD)                   | 157.1 (40.2)    | 152.0 (32.1)  | 46.3 (13.3)     | 46.8 (10.9)    | 156.1 (39.2)                  | 149.7 (30.0)           |
| LDL (mg/dl), mean (SD)                   | 48.0 (13.0)*    | 42.9 (11.8)*  | 73.0 (18.5)*    | 132.7 (20.9)*  | 47.0 (13.1)                   | 42.8 (10.2)            |
| Triglycerides (mg/dl), mean (SD)         | 87.2 (32.5)     | 85.7 (28.2)   | 103.6 (50.2)*   | 139.5 (67.4)*  | 86.4 (32.3)                   | 86.0 (26.2)            |
| Lipoprotein A (mg/dl), mean (SD)         | 109.5 (59.6)    | 117.0 (49.5)  | 19.5 (21.0)*    | 36.3 (39.0)*   | 115.7 (70.5)                  | 104.9 (35.7)           |
| Mean-max common IMT (mm), mean (SD)      | 24.4 (29.5)     | 20.9 (20.0)   | 0.469 (0.043)   | 0.467 (0.041)  | 23.3 (28.0)                   | 22.2 (19.7)            |
| Mean-max IMT (mm), mean (SD)             | 0.467 (0.043)   | 0.474 (0.041) | 0.585 (0.057)   | 0.579 (0.055)  | 0.468 (0.043)                 | 0.466 (0.038)          |

| Variable                         | hsCRP         |               | LDL           |               | hsCRP/pubertal status         |                        |
|----------------------------------|---------------|---------------|---------------|---------------|-------------------------------|------------------------|
|                                  | <1.5 mg/l     | 1.5 mg/l      | <110 (mg/dl)  | 110 (mg/dl)   | Not ( 1.5 mg/l post-pubertal) | 1.5 mg/l post-pubertal |
| Mean-maximal IMT (mm), mean (SD) | 0.582 (0.058) | 0.587 (0.051) | 0.583 (0.057) | 0.584 (0.050) | 0.583 (0.057)                 | 0.584 (0.050)          |

\* p<0.05 for the comparison between subgroup treatment arms.

† Current use of methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide or rituximab.

BMI, body mass index; HDL, high density lipoprotein cholesterol; hsCRP, high sensitivity C reactive protein; Hx, history of; IMT, intima medial thickening; LDL, low density lipoprotein cholesterol; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

**Table 3**  
 Comparison of atorvastatin and placebo treatment effects on CIMT progression in subgroups defined by pubertal status

| CIMT measurements     | Pre-pubertal        |   |  | Pubertal |   |  |         |
|-----------------------|---------------------|---|--|----------|---|--|---------|
|                       | Interaction p value | Progression rate of atorvastatin estimates (95% CI) | Progression rate of placebo estimates (95% CI) | p Value  | Progression rate of atorvastatin estimates (95% CI) | Progression rate of placebo estimates (95% CI) | p Value |
| Mean-mean common      | 0.149               | 0.0025 (-0.0002 to 0.0051)                          | 0.0017 (-0.0012 to 0.0045)                     | 0.684    | 0.0001 (-0.0019 to 0.0021)                          | 0.0029 (0.0008 to 0.0049)                      | 0.061   |
| Mean-max              | 0.101               | 0.0054 (0.0019 to 0.0090)                           | 0.0049 (0.0011 to 0.0086)                      | 0.828    | 0.0026 (-0.0001 to 0.0053)                          | 0.0074 (0.0047 to 0.0101)                      | 0.014   |
| Mean-mean             | 0.056               | 0.0050 (0.0026 to 0.0074)                           | 0.0040 (0.0015 to 0.0065)                      | 0.579    | 0.0023 (0.0005 to 0.0041)                           | 0.0055 (0.0037 to 0.0073)                      | 0.014   |
| Mean-max common       | 0.440               | 0.0022 (-0.0019 to 0.0062)                          | 0.0006 (-0.0036 to 0.0049)                     | 0.609    | -0.0003 (-0.0033 to 0.0028)                         | 0.0011 (-0.0020 to 0.0041)                     | 0.544   |
| Mean-max internal     | 0.063               | 0.0138 (0.0076 to 0.0200)                           | 0.0126 (0.0061 to 0.0192)                      | 0.795    | 0.0062 (0.0015 to 0.0110)                           | 0.0157 (0.0110 to 0.0204)                      | 0.006   |
| Mean-mean internal    | 0.186               | 0.0087 (0.0044 to 0.0129)                           | 0.0071 (0.0025 to 0.0116)                      | 0.613    | 0.0056 (0.0023 to 0.0088)                           | 0.0092 (0.0059 to 0.0124)                      | 0.124   |
| Mean-max bifurcation  | 0.100               | 0.0039 (-0.0013 to 0.0091)                          | 0.0030 (-0.0025 to 0.0085)                     | 0.817    | 0.0029 (-0.0010 to 0.0068)                          | 0.0099 (0.0059 to 0.0138)                      | 0.014   |
| Mean-mean bifurcation | 0.019               | 0.0056 (0.0023 to 0.0090)                           | 0.0037 (0.0002 to 0.0073)                      | 0.441    | 0.0014 (-0.0011 to 0.0040)                          | 0.0067 (0.0042 to 0.0093)                      | 0.004   |
| Mean-max far wall     | 0.500               | 0.0047 (0.0003 to 0.0092)                           | 0.0066 (0.0019 to 0.0113)                      | 0.569    | 0.0044 (0.0011 to 0.0078)                           | 0.0091 (0.0057 to 0.0124)                      | 0.057   |
| Mean-mean far wall    | 0.359               | 0.0048 (0.0020 to 0.0076)                           | 0.0055 (0.0025 to 0.0084)                      | 0.750    | 0.0039 (0.0018 to 0.0061)                           | 0.0070 (0.0048 to 0.0091)                      | 0.049   |
| Mean-max near wall    | 0.027               | 0.0062 (0.0017 to 0.0106)                           | 0.0021 (-0.0026 to 0.0068)                     | 0.223    | 0.0003 (-0.0031 to 0.0037)                          | 0.0054 (0.0020 to 0.0088)                      | 0.038   |
| Mean-mean near wall   | 0.021               | 0.0052 (0.0021 to 0.0084)                           | 0.0018 (-0.0016 to 0.0051)                     | 0.140    | 0.0004 (-0.0020 to 0.0028)                          | 0.0037 (0.0013 to 0.0061)                      | 0.058   |

The interaction p value assesses differences in the progression rate for atorvastatin/placebo and subgroups. The p values in the pre-pubertal and pubertal groups assess differences in the progression rate for atorvastatin/placebo groups. CIMT, carotid intima media thickness.

**Table 4**  
 Comparison of atorvastatin and placebo treatment effects on CIMT progression in subgroups defined by hsCRP

| CIMT measurements     | hsCRP < 1.5 mg/l    |   |  | hsCRP 1.5 mg/l |   |  |         |
|-----------------------|---------------------|---|--|----------------|---|--|---------|
|                       | Interaction p value | Progression rate of atorvastatin estimates (95% CI) | Progression rate of placebo estimates (95% CI) | p Value        | Progression rate of atorvastatin estimates (95% CI) | Progression rate of placebo estimates (95% CI) | p Value |
| Mean-mean common      | 0.049               | 0.0015 (-0.0005 to 0.0035)                          | 0.0011 (-0.0009 to 0.0031)                     | 0.795          | -0.0007 (-0.0036 to 0.0023)                         | 0.0042 (0.0010 to 0.0075)                      | 0.029   |
| Mean-max              | 0.413               | 0.0025 (-0.0002 to 0.0052)                          | 0.0043 (0.0016 to 0.0069)                      | 0.357          | 0.0055 (0.0016 to 0.0094)                           | 0.0102 (0.0059 to 0.0145)                      | 0.117   |
| Mean-mean             | 0.093               | 0.0025 (0.0007 to 0.0043)                           | 0.0031 (0.0014 to 0.0049)                      | 0.633          | 0.0041 (0.0015 to 0.0067)                           | 0.0087 (0.0058 to 0.0115)                      | 0.021   |
| Mean-max common       | 0.710               | 0.0002 (-0.0028 to 0.0032)                          | -0.0004 (-0.0035 to 0.0026)                    | 0.769          | 0.0013 (-0.0032 to 0.0057)                          | 0.0021 (-0.0028 to 0.0070)                     | 0.801   |
| Mean-max internal     | 0.879               | 0.0047 (0.0001 to 0.0093)                           | 0.0099 (0.0053 to 0.0146)                      | 0.114          | 0.0174 (0.0107 to 0.0242)                           | 0.0236 (0.0161 to 0.0311)                      | 0.231   |
| Mean-mean internal    | 0.919               | 0.0032 (0.0000 to 0.0064)                           | 0.0057 (0.0025 to 0.0089)                      | 0.277          | 0.0125 (0.0078 to 0.0171)                           | 0.0154 (0.0102 to 0.0206)                      | 0.412   |
| Mean-max bifurcation  | 0.232               | 0.0039 (-0.0000 to 0.0079)                          | 0.0061 (0.0021 to 0.0100)                      | 0.445          | 0.0014 (-0.0044 to 0.0072)                          | 0.0099 (0.0035 to 0.0163)                      | 0.056   |
| Mean-mean bifurcation | 0.176               | 0.0028 (0.0003 to 0.0053)                           | 0.0042 (0.0017 to 0.0068)                      | 0.435          | 0.0030 (-0.0007 to 0.0067)                          | 0.0089 (0.0048 to 0.0129)                      | 0.035   |
| Mean-max far wall     | 0.831               | 0.0028 (-0.0005 to 0.0061)                          | 0.0063 (0.0030 to 0.0096)                      | 0.143          | 0.0080 (0.0031 to 0.0128)                           | 0.0105 (0.0051 to 0.0159)                      | 0.489   |
| Mean-mean far wall    | 0.858               | 0.0031 (0.0010 to 0.0052)                           | 0.0052 (0.0031 to 0.0073)                      | 0.155          | 0.0062 (0.0031 to 0.0093)                           | 0.0089 (0.0055 to 0.0123)                      | 0.258   |
| Mean-max near wall    | 0.087               | 0.0019 (-0.0014 to 0.0053)                          | 0.0013 (-0.0021 to 0.0047)                     | 0.796          | 0.0026 (-0.0024 to 0.0076)                          | 0.0097 (0.0042 to 0.0152)                      | 0.062   |
| Mean-mean near wall   | 0.011               | 0.0019 (-0.0005 to 0.0042)                          | 0.0003 (-0.0020 to 0.0027)                     | 0.370          | 0.0017 (-0.0018 to 0.0052)                          | 0.0082 (0.0043 to 0.0120)                      | 0.014   |

The interaction p value assesses differences in the progression rate for atorvastatin/placebo and subgroups.

The p values in the hsCRP < 1.5 mg/l and hsCRP 1.5 mg/l groups assess differences in the progression rate for atorvastatin/placebo groups. CIMT, carotid intima media thickness; hsCRP, high sensitivity C reactive protein.

**Table 5**  
 Comparison of atorvastatin and placebo treatment effects on CIMT progression in subgroups defined by pubertal status and hsCRP

| CIMT measurements     | Not (pubertal and hsCRP 1.5 mg/l) |   |  | Pubertal and hsCRP 1.5 mg/l |   |  |         |
|-----------------------|-----------------------------------|---|--|-----------------------------|---|--|---------|
|                       | Interaction p value               | Progression rate of atorvastatin estimates (95% CI) | Progression rate of placebo estimates (95% CI) | p Value                     | Progression rate of atorvastatin estimates (95% CI) | Progression rate of placebo estimates (95% CI) | p Value |
| Mean-mean common      | 0.005                             | 0.0015 (-0.0004 to 0.0033)                          | 0.0014 (-0.0005 to 0.0032)                     | 0.946                       | -0.0028 (-0.0070 to 0.0015)                         | 0.0071 (0.0023 to 0.0118)                      | 0.002   |
| Mean-max              | 0.156                             | 0.0032 (0.0008 to 0.0056)                           | 0.0051 (0.0026 to 0.0075)                      | 0.296                       | 0.0044 (-0.0011 to 0.0100)                          | 0.0128 (0.0065 to 0.0191)                      | 0.050   |
| Mean-mean             | 0.008                             | 0.0030 (0.0014 to 0.0046)                           | 0.0037 (0.0021 to 0.0054)                      | 0.530                       | 0.0031 (-0.0007 to 0.0068)                          | 0.0119 (0.0078 to 0.0161)                      | 0.002   |
| Mean-max common       | 0.194                             | 0.0009 (-0.0018 to 0.0036)                          | -0.0001 (-0.0029 to 0.0027)                    | 0.613                       | -0.0016 (-0.0079 to 0.0047)                         | 0.0042 (-0.0029 to 0.0113)                     | 0.231   |
| Mean-max internal     | 0.121                             | 0.0081 (0.0040 to 0.0123)                           | 0.0116 (0.0073 to 0.0159)                      | 0.251                       | 0.0120 (0.0024 to 0.0216)                           | 0.0279 (0.0170 to 0.0387)                      | 0.032   |
| Mean-mean internal    | 0.159                             | 0.0054 (0.0025 to 0.0083)                           | 0.0069 (0.0039 to 0.0098)                      | 0.488                       | 0.0099 (0.0032 to 0.0165)                           | 0.0191 (0.0116 to 0.0266)                      | 0.071   |
| Mean-max bifurcation  | 0.382                             | 0.0028 (-0.0007 to 0.0063)                          | 0.0064 (0.0028 to 0.0100)                      | 0.161                       | 0.0046 (-0.0036 to 0.0128)                          | 0.0142 (0.0049 to 0.0234)                      | 0.129   |
| Mean-mean bifurcation | 0.023                             | 0.0029 (0.0006 to 0.0051)                           | 0.0044 (0.0021 to 0.0067)                      | 0.347                       | 0.0027 (-0.0025 to 0.0079)                          | 0.0141 (0.0082 to 0.0200)                      | 0.005   |
| Mean-max far wall     | 0.790                             | 0.0036 (0.0006 to 0.0066)                           | 0.0066 (0.0035 to 0.0096)                      | 0.177                       | 0.0086 (0.0017 to 0.0155)                           | 0.0131 (0.0053 to 0.0209)                      | 0.401   |
| Mean-mean far wall    | 0.259                             | 0.0036 (0.0017 to 0.0055)                           | 0.0054 (0.0035 to 0.0073)                      | 0.200                       | 0.0064 (0.0020 to 0.0108)                           | 0.0123 (0.0073 to 0.0172)                      | 0.082   |
| Mean-max near wall    | 0.029                             | 0.0026 (-0.0004 to 0.0056)                          | 0.0028 (-0.0003 to 0.0059)                     | 0.921                       | -0.0004 (-0.0074 to 0.0066)                         | 0.0126 (0.0046 to 0.0205)                      | 0.016   |
| Mean-mean near wall   | 0.002                             | 0.0023 (0.0001 to 0.0044)                           | 0.0015 (-0.0007 to 0.0037)                     | 0.621                       | -0.0007 (-0.0057 to 0.0042)                         | 0.0112 (0.0057 to 0.0168)                      | 0.002   |

The interaction p value assesses differences in the progression rate for atorvastatin/placebo and subgroups. The p values in the 'not (pubertal and hsCRP 1.5 mg/l)' and 'pubertal and hsCRP 1.5 mg/l' groups assess differences in the progression rate for atorvastatin/placebo groups.

CIMT, carotid intima media thickness; hsCRP, high sensitivity C reactive protein.