Pediatric implications of heterozygous familial hypercholesterolemia

Wiegman, A.

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Chapter 8

Statin Therapy in Hypercholesterolemic Children
Long-term Efficacy and Safety

Albert Wiegman¹,², Barbara A. Hutten³, Eric de Groot¹,
Jessica Rodenburg¹, Henk D. Bakker², Harry R. Büller¹,
Eric J.G. Sijbrands⁴, John J.P. Kastelein¹

¹Departments of Vascular Medicine, ²Paediatrics, and ³Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, The Netherlands
⁴Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

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Chapter 8

Abstract

Background

Children with familial hypercholesterolemia (FH) have endothelial dysfunction and increased carotid intima-media thickness (IMT) as heralds of the premature atherosclerotic disease they will suffer later in life. Although intervention in the causal pathway of this disorder has been available for over a decade, the long-term efficacy and safety of cholesterol-lowering medication has not been evaluated in children.

Methods

We performed a randomized, double-blind, placebo-controlled, two-year trial of daily treatment with pravastatin 20 - 40 mg in 214 FH children, aged between 8 and 18 years. The primary efficacy outcome was defined as the change from baseline in mean carotid IMT over two years, whereas the principal safety outcome was measurement of growth, maturation and hormone levels over two years as well as changes of levels of muscle and liver enzymes.

Results

Compared to baseline, carotid IMT showed regression on pravastatin (Δ IMT: -0.010 ± 0.048 mm), whereas progression was observed in the placebo group (Δ IMT: +0.005 ± 0.044 mm). The change of IMT between the two groups (0.014 ± 0.046 mm) differed significantly (p=0.019). No differences were observed for growth or endocrine function parameters, Tanner staging scores (genitals/breasts and pubic hair), and onset of menses or in testicular volume between the two groups.

Conclusions

Two years of pravastatin induced a significant regression of carotid atherosclerosis in FH children with no adverse effects on growth, sexual maturation, hormone levels, liver or muscle tissue.
Introduction

Familial hypercholesterolemia (FH) is the paradigm of the established relationship between increased low-density lipoprotein cholesterol (LDL-C) and cardiovascular disease. This monogenic disorder is characterized by exposure to severely elevated LDL-C levels from birth onwards. Endothelial function, measured as flow-mediated dilatation of the brachial artery, is already impaired in prepubertal children with FH. In addition to these early functional changes, accumulation of LDL-C in FH children deteriorates the vascular morphology and gives rise to an increased intima-media thickness (IMT) of the carotid arteries. As a sequel to these observations, myocardial ischemia and coronary artery stenoses have been documented in young adults with this disorder. The sequence of events in these untreated children is likely to proceed from endothelial dysfunction to increased arterial wall thickness and finally to clinically important coronary stenoses often in a time span of less than three decades.

Upon diagnosis, adult FH patients are prescribed lifelong treatment with inhibitors of hydroxymethylglutarylco-enzyme A-reductase (statins), but postponing statin treatment until adulthood might allow the development of significant arterial lesions in young FH patients. Accordingly, early initiation of statin treatment in FH children might be advantageous, but unfortunately, studies of such treatment have so far only addressed short-term tolerability and safety.

Carotid IMT represents the combined intima and media thickness of the arterial wall and numerous studies have shown that this surrogate marker of atherosclerotic vessel wall change is sensitive to risk intervention and constitutes a reliable indicator of clinical outcomes.

Given the effects of statins on endogenous cholesterol biosynthesis, the danger might arise that growth and sexual development are negatively influenced by long-term exposure to these drugs in children. We therefore performed a placebo controlled, randomized, clinical trial with pravastatin in 8 to 18 year old FH children and we used carotid IMT to measure efficacy outcome and growth and maturation to assess the safety of long-term exposure to such medication.

Methods

Patients

Children were eligible when they met the following criteria: one parent with a definite clinical or molecular diagnosis of FH, age between 8 and 18 years; two fasting samples with LDL-C levels above or equal to 4.0 mmol/l and triglyceride levels below 4.0 mmol/l; adequate contraception in sexually active girls and no drug treatment for their FH. Reasons for exclusion were homozygous FH, hypothyroidism and abnormal levels of
muscle or liver enzymes. The study protocol was approved by the Institutional Review
Board. Written informed consent was obtained from all children and their parents.

Study design
The study, a prospective, randomized, double-blind, placebo-controlled trial in children
with heterozygous FH, recruited subjects between 1998 and 2000 at the Academic
Medical Center, Amsterdam, The Netherlands. All children were instructed to continue
a fat restricted diet and to maintain habitual physical activity during the trial. Consenting
FH children were randomly assigned to receive either pravastatin or placebo. In the
active treatment group, children younger than 14 years of age received 20 mg
pravastatin, whereas those 14 years and older received 40 mg pravastatin daily. Study
drug compliance was monitored by tablet counting.

Primary Efficacy Outcome: Intima-Media Thickness
The primary efficacy outcome of this study was defined as the change from baseline
in mean carotid IMT between the pravastatin and placebo groups at two years of
follow-up. Mean carotid IMT was defined as the mean IMT of the right and left
common carotid (CCA), the carotid bulb (BULB) and the internal carotid (ICA) far wall
segments. All B-mode ultrasound examinations were performed by a single experienced
sonographer. IMT measurements were performed at entry and after one and two
years of follow-up.

An Acuson 128XP/10v (Acuson Corporation, Mountain View, CA) ultrasound
instrument equipped with a 5-10 MHz L7 (Acuson L7) and Extended Frequency
software was used. The left and right far walls of the carotid artery segments were
imaged in a standardized magnification (2 x 2 cm). The sonographer saved a video
still image of each segment as a 4:1 compressed JPEG file (SONY DKR-700P video still
image recorder). The digital images were analyzed off-line by one image analyst. For
image analysis, e-track software was used, as previously published. For a given
segment, IMT was defined as the average of the right and left IMT measurements. If
on either side a segment was missing, IMT was defined as the value of the remaining
segment: if both left and right side values were unavailable, the IMT value was
considered missing for that segment and in that situation also the mean carotid IMT
was considered missing.

Lipids and Lipoproteins
Blood samples for measurement of lipids and lipoproteins were collected after at
least a 12 hour overnight at the same timepoints as for liver and muscle enzymes.
Lipids, lipoproteins, apolipoprotein A1 and B, and lipoprotein(a) levels were measured
with standard (automated) methods. LDL-C levels were calculated using the Friedewald
equation. Mutations in the LDL-receptor gene were detected as previously described.
Principal Safety Outcome

To measure deleterious effects on maturation and/or growth, we measured the levels of sex steroids, gonadotrophins and parameters of the pituitary-adrenal axis at baseline and at one and two years. Secondly, measurements of the children's height, weight, body surface area,22 Tanner staging (genitals/breasts and pubic hair), menarche and testicular volume were obtained at the same time points to assess adverse effects of pravastatin on growth and development. To detect potential side effects on muscle and liver, hepatic enzymes; alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT), and creatine phosphokinase (CPK) as well as muscle complaints were assessed at baseline, at three month intervals the first year and at 6 month intervals the second year.

Sample size calculation

Prior to the trial, replicate ultrasound measurements were performed in 20 FH children and 20 unaffected siblings. The standard deviation (σ) of the means of the differences of the paired repeated combined carotid IMT measurements was 0.045 mm (σFH and σSI BB were similar). A sample size N for an effect size Δ and the σ was calculated according to $N=2[(Z_α+Z_β)\sigma/Δ]^2$. We set the two-sided α (type 1 error) at 0.05 and the β (type II error) at 0.1 (power 90%). Based on these assumptions the sample for an effect size of 0.02 mm IMT was two groups of approx. 100 children.

Statistical Analyses

Differences in IMT between the treatment groups in terms of change from baseline after 24 months were analyzed with analysis of covariance (ANCOVA), in which the independent variables were treatment group and baseline IMT. In addition, several multivariate models were built to explore the effect of age, gender and interaction terms. Treatment differences in change from baseline after 24 months in terms of lipids, lipoproteins, apolipoproteins and safety measurements (hormones, liver and muscle enzymes, height, weight and testicular volume) were analyzed with ANCOVA, adjustments were made for baseline values. Data with a skewed distribution were first log-transformed. Occurrences of moderate elevations of ASAT, ALAT and CPK during two years of treatment were compared with Fisher's exact test. Furthermore, mixed model ANOVA with (linear) time and treatment effects and their interaction were used to assess the rate of changes in ASAT, ALAT and CPK during follow-up.

At baseline, mean values between the treatment groups were compared using a t-test; data with a skewed distribution were first log-transformed. Chi square tests were applied for comparing distributions of dichotomous data between the groups.

Analyses were interpreted at the two-sided significance level of 0.05. Statistical
analyses were done with SAS (release 8.02, SAS Institute Inc, Cary, NC, USA).

Results

Characteristics of the FH Children
Between 1998 and 2000, 274 consecutive and untreated children, whose initial LDL-C levels were above or equal to 4.0 mmol/l, were referred in case his/her parent was diagnosed with definite FH. Of these, 265 children were eligible according to the inclusion criteria, while in 9 children the second LDL-C level was below 4.0 mmol/l. In 44 cases parent, child or both declined participation, which left 221 potential study participants. Seven of these children had to be excluded for different reasons: homozygous FH (n=3), hypothyroidism (n=1), hypertriglyceridemia (n=1) and persistently elevated levels of muscle or liver enzymes (n=2).

Thus, 214 children (100 boys and 114 girls) were randomized: 106 to pravastatin and 108 to placebo. The mean age was 13.0 years (range 8.0-18.5 years). In 201 children (94%), the diagnosis of FH was confirmed by characterization of the mutation in the LDL receptor gene. Baseline characteristics were similar in the two study groups with respect to age, smoking frequency, systolic and diastolic blood pressure, gender distribution, and in girls, menarche (data not shown).

Ten children (all girls: 5 on pravastatin and 5 on placebo) discontinued the study prematurely, because they withdrew consent. However, only three of them were lost...
Statin Therapy in Hypercholesterolemic Children Long-term Efficacy and Safety

to follow-up (two children in the treatment and one in the placebo group). Their lipids, IMT, and safety parameters were included in the primary efficacy outcome and principal safety outcome as collected until discontinuation.

Primary Efficacy Outcome: Intima-Media Thickness
At baseline, the means of the separate carotid IMT segments (data not shown) as well as the combined IMT were similar in the pravastatin and placebo group (Table 1). The IMT changes of the separate segments are summarized in figure 1. All three segments of the carotid arterial wall showed a trend towards regression of IMT after two years of pravastatin, while these segments exhibited a trend towards progression in the placebo treated patients. The mean combined carotid IMT exhibited significant regression after two years treatment with pravastatin (Δ IMT: -0.010 ± 0.048 mm) compared to progression of the mean carotid IMT in the placebo group (Δ IMT: +0.005 ± 0.044 mm). The change in carotid IMT (0.014 ± 0.046 mm) differed significantly between the two groups (p=0.019). Multivariate analyses showed that neither gender nor age significantly influenced these results.

Changes in mean carotid IMT from baseline between the two treatment groups were compared under the assumption that the children were independent. However, in some cases more than one child per family was included, and consequently, data

Table 1. Mean Changes from Baseline for Intima Media Thickness of Carotid Artery Segments and Lipids and Lipoproteins in the Two Study Groups after Two Years

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change from baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pravastatin</td>
<td>Placebo</td>
<td>Pravastatin</td>
</tr>
<tr>
<td>Mean Carotid IMT (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA + BULB + ICA</td>
<td>0.497 ± 0.055</td>
<td>0.492 ± 0.045</td>
<td>-0.010 ± 0.048</td>
</tr>
<tr>
<td>Lipids (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>7.82 ± 1.45</td>
<td>7.75 ± 1.21</td>
<td>-1.44 ± 1.10</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>6.17 ±1.38</td>
<td>6.13 ± 1.20</td>
<td>-1.47 ± 1.04</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>1.22 ± 0.26</td>
<td>1.25 ± 0.29</td>
<td>0.08 ± 0.26</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>0.79 [0.56,1.26]</td>
<td>0.72 [0.52,1.02]</td>
<td>-0.14 [0.39,0.18]</td>
</tr>
<tr>
<td>(Apo)Lipoproteins (g/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipoprotein(a)*</td>
<td>0.13 [0.06,0.32]</td>
<td>0.12 [0.04,0.24]</td>
<td>0.01 [0.00,0.05]</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>1.04 ± 0.14</td>
<td>1.05 ± 0.15</td>
<td>0.05 ± 0.14</td>
</tr>
<tr>
<td>Apolipoprotein B100</td>
<td>1.42 ± 0.35</td>
<td>1.40 ± 0.26</td>
<td>-0.27 ± 0.27</td>
</tr>
</tbody>
</table>

Values are given as means ± standard deviation, *triglycerides and lipoprotein(a) are given as medians and interquartile range; CCA=common carotid artery; BULB=carotid bulb; ICA=internal carotid artery; LDL=low-density lipoprotein; HDL=high-density lipoprotein
<table>
<thead>
<tr>
<th></th>
<th>Baseline Pravastatin n=106</th>
<th>Placebo n=108</th>
<th>Change from baseline</th>
<th>Baseline Pravastatin n=104</th>
<th>Placebo n=107</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156 ± 16</td>
<td>157 ± 13</td>
<td>8 ± 6</td>
<td>8 ± 6</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>49.1 ± 15.5</td>
<td>49.7 ± 14.7</td>
<td>8.0 ± 5.8</td>
<td>7.8 ± 5.5</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.5 ± 3.4</td>
<td>19.7 ± 3.8</td>
<td>1.3 ± 1.6</td>
<td>1.3 ± 1.3</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.44 ± 0.31</td>
<td>1.46 ± 0.28</td>
<td>0.16 ± 0.10</td>
<td>0.15 ± 0.11</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Testicular volume</td>
<td>4.0 [2.0,13.8]</td>
<td>4.0 [3.0,15.5]</td>
<td>2.3 [1.0,13.8]</td>
<td>3.0 [1.5,6.5]</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td><strong>Liver and muscle enzymes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAT</td>
<td>21 [16,27]</td>
<td>22 [17,26]</td>
<td>2 [-2,5]</td>
<td>2 [-2,5]</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>ALAT</td>
<td>13 [12,18]</td>
<td>14 [11,18]</td>
<td>0 [-4,4]</td>
<td>0 [5,4]</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>CPK</td>
<td>100 [77,144]</td>
<td>102 [75,145]</td>
<td>-4 [-20,11]</td>
<td>-3 [-22,20]</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>28 [18,39]</td>
<td>27 [20,40]</td>
<td>1 [9,11]</td>
<td>0 [-7,6]</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>240 [180,340]</td>
<td>240 [190,310]</td>
<td>-10 [-70,60]</td>
<td>10 [60,110]</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>DHEAs</td>
<td>2.4 [1.5,3.7]</td>
<td>2.9 [1.8,4.8]</td>
<td>0.6 [0.0,1.4]</td>
<td>0.7 [0.1,1.5]</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>1.7 [0.6,3.8]</td>
<td>1.8 [1.0,3.6]</td>
<td>0.2 [-0.5,1.4]</td>
<td>0.4 [-0.8,1.8]</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>LH</td>
<td>1.1 [0.5,3.3]</td>
<td>0.5 [0.5,3.5]</td>
<td>0.2 [0.0,1.7]</td>
<td>0.1 [0.0,1.3]</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>2.1 [1.3,2.7]</td>
<td>2.0 [1.5,2.8]</td>
<td>-0.3 [-0.7,0.4]</td>
<td>-0.1 [-0.7,0.4]</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>17β-estradiol (girls)</td>
<td>0.05 [0.05,0.14]</td>
<td>0.05 [0.05,0.16]</td>
<td>0 [0.01,0.09]</td>
<td>0 [0.07,0.09]</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Testosterone (boys)</td>
<td>1.4 [0.4,16.0]</td>
<td>2.3 [0.4,17.5]</td>
<td>4.1 [0.0,11.3]</td>
<td>2.4 [0.0,8.9]</td>
<td>0.68</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as means ± standard deviation or, in case of a skewed distribution as medians and interquartile ranges; BMI = body mass index; BSA = body surface area; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; CPK = creatine phosphokinase; ACTH = adrenocorticotropic hormone; DHEAs = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.  

were related to a small extent. This could have resulted in a bias of the standard errors and p-values. Therefore, the data were also analyzed with linear regression analysis adjusted for family number using generalized estimating equations (GEE) in the GENMOD procedure of SAS. Although the overall results differed marginally from the ANCOVA analysis, the difference in changes for the CCA segment between the two groups now became statistically significant (p-value changed from 0.061 into 0.038), and the difference of the changes in the mean combined carotid IMT became statistically slightly more pronounced (p-value from 0.019 into 0.012).  

**Lipid and Lipoprotein Levels**

As expected, pravastatin significantly reduced mean LDL-C levels compared to placebo (-24.1% versus +0.3%, respectively; p<0.0001; absolute differences are shown in
Table 3. Tanner Stage Changes from Baseline to Two Years

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No change in classification level</th>
<th>Changed ≥1 classification level</th>
<th>Between treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>55</td>
<td>19 (35%)</td>
<td>36</td>
</tr>
<tr>
<td>Placebo</td>
<td>56</td>
<td>22 (39%)</td>
<td>34</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>49</td>
<td>22 (45%)</td>
<td>27</td>
</tr>
<tr>
<td>Placebo</td>
<td>50</td>
<td>16 (32%)</td>
<td>34</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>104</td>
<td>41 (35%)</td>
<td>63</td>
</tr>
<tr>
<td>Placebo</td>
<td>106</td>
<td>38 (36%)</td>
<td>68</td>
</tr>
</tbody>
</table>

Table 1), which was maintained over the two year study period (Table 1). In line with this, apolipoprotein B was also significantly decreased by pravastatin. HDL-C and triglyceride levels did not change significantly in the pravastatin treated children. However, a small but significant increase in apolipoprotein A1 was observed in the pravastatin treated children.

Safety and Tolerability

The height of the children increased similarly in the pravastatin and the placebo group (7.9 ± 5.7 and 7.8 ± 6.1 cm, respectively). Weight increased 8.0 ± 5.8 kg in the pravastatin group and 7.8 ± 5.5 kg in the placebo group (Table 2). During the two years of follow-up changes in testicular volume, change in Tanner staging scores and menarche were not different between the groups (Tables 2 and 3).

All endocrine function parameters at entry and after two years were similar between pravastatin and placebo groups (Table 2). At the end of the trial, no relevant differences with respect to changes from baseline were observed for either ASAT, ALAT or CPK (Table 2). A more than three times elevation in levels of ASAT or ALAT, and a more than four times elevation in CPK occurred seldom and was equally distributed between the pravastatin and placebo groups. There was also no difference between the two groups with respect to the rate of changes of ASAT, ALAT or CPK during follow-up. One child had an asymptomatic but extreme CPK elevation (16.400 U/L) after 168 days of study therapy. Within one week after stopping the study drug, CPK fell to normal values and, thereafter, the study drug was reintroduced, and at end of trial, turned out to be placebo.
Although the sample size for this trial was based on the primary outcome (change from baseline in mean carotid IMT after two years follow-up), the study was of sufficient size to detect clinically relevant differences in a number of safety parameters between the two study groups.

Discussion

In this randomized, double-blind, placebo-controlled study, we assessed the two-year efficacy and safety of pravastatin therapy in children with FH. In these children, the severe hypercholesterolemia that results from this monogenic disorder constitutes the major determinant of atherosclerotic risk. We were able to show that statin treatment in this pediatric FH population indeed improved the lipoprotein profile towards a more physiological situation and, consequently, we observed regression of carotid IMT. This shows that the increased arterial wall thickness progression found in FH children is reversible. Moreover, we extensively analyzed possible adverse events and untoward influences on growth and maturation of the children and none were observed with pravastatin.

The long-term tolerability of this drug in these children was excellent. Discontinuation of the study protocol was a rare event and equally distributed between the active medication and placebo groups. Severe adverse effects on liver and muscle were not observed and after two years the levels of the hepatic and muscle enzymes did not differ between the two groups. So far, only a few studies have evaluated statin treatment in FH children.\textsuperscript{11,15} These studies showed promising short-term efficacy and reassuring safety in terms of changes of hepatic and muscle enzymes. In contrast, our results are based on long-term follow-up and on safety measurement with a much broader perspective. In particular, levels of DHEAS and cortisol were unchanged after two years of pravastatin, while a previous study using simvastatin did show mild changes with HMG-CoA reductase inhibition.\textsuperscript{14}

Several methodological aspects of our study require comment. Since carotid IMT progression in placebo treated children was less than expected, our study might have actually underestimated the efficacy of pravastatin in FH children. This attenuated progression in the placebo group is likely the consequence of strict adherence to a healthy lifestyle including diet, sports and a very low frequency of cigarette smoking.

Furthermore, we used carotid IMT as a surrogate marker of future vascular disease, but there is solid evidence that changes in arterial wall IMT are predictive for cardiovascular outcome.\textsuperscript{16,18}

To limit IMT measurement variability we have used a single ultrasound machine, one sonographer and a single reader. To reduce variability even further, image analysis software automatically investigated each IMT measurement and accounted for the
videoline interpolation of the ultrasound equipment. In addition, the double-blind design ensured that all study personnel was unaware of treatment allocation.

Nevertheless, our findings cannot be extrapolated to children with an increased atherosclerotic risk as a result of disorders other than FH. In FH children, IMT likely constitutes a strong marker of (future) risk because it is part of the pathophysiological pathway from severe hypercholesterolemia to endothelial dysfunction, early atherosclerosis and premature onset of CVD. Our IMT findings and the observed efficacy of pravastatin treatment should therefore be restricted to children with FH. We have devoted major efforts to include a representative FH population: consecutively referred patients; a molecularly heterogeneous group; a wide age range stretching from prepuberty into adolescence and very limited exclusion criteria which resulted in the exclusion of only a small number from the eligible children. We feel, accordingly, that our study results are valid for FH children in general.

In conclusion, two years of pravastatin induced regression of carotid atherosclerosis in FH children with no adverse effects on liver, muscle, growth or sexual maturation.

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