Efficacy and Safety of Statin Therapy in Children With Familial Hypercholesterolemia
A Randomized Controlled Trial

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F AMILIAL HYPERCHOLESTEROL-emia is the paradigm of the established relationship between increased low-density lipoprotein cholesterol (LDL-C) and cardiovascular disease.[1,2] This monogenic disorder is characterized by exposure to severely elevated LDL-C levels from birth onward.[3,4] Endothelial function, measured as flow-mediated dilatation of the brachial artery, is already impaired in prepubertal children with familial hypercholesterolemia.[5] In addition to these early functional changes, accumulation of LDL-C in children with familial hypercholesterolemia leads to deterioration of the vascular morphology and gives rise to increased intima-media thickness (IMT) of the carotid arteries.[6-9] As a sequel to these observations, myocardial ischemia and coronary artery stenoses have been documented in young adults with this disorder.[10,11] The sequence of events in untreated children proceeds from endothelial dysfunction to increased

For editorial comment see p 377.

Context Children with familial hypercholesterolemia have endothelial dysfunction and increased carotid intima-media thickness (IMT), which herald the premature atherosclerotic disease they develop later in life. Although intervention therapy in the causal pathway of this disorder has been available for more than a decade, the long-term efficacy and safety of cholesterol-lowering medication have not been evaluated in children.

Objective To determine the 2-year efficacy and safety of pravastatin therapy in children with familial hypercholesterolemia.

Design Randomized, double-blind, placebo-controlled trial that recruited children between December 7, 1997, and October 4, 1999, and followed them up for 2 years.

Setting and Participants Two hundred fourteen children with familial hypercholesterolemia, aged 8 to 18 years and recruited from an academic medical referral center in the Netherlands.

Intervention After initiation of a fat-restricted diet and encouragement of regular physical activity, children were randomly assigned to receive treatment with pravastatin, 20 to 40 mg/d (n=106), or a placebo tablet (n=108).

Main Outcome Measures The primary efficacy outcome was the change from baseline in mean carotid IMT compared between the 2 groups over 2 years; the principal safety outcomes were growth, maturation, and hormone level measurements over 2 years as well as changes in muscle and liver enzyme levels.

Results Compared with baseline, carotid IMT showed a trend toward regression with pravastatin (mean [SD], −0.010 [0.048] mm; P=.049), whereas a trend toward progression was observed in the placebo group (mean [SD], +0.005 [0.044] mm; P=.28). The mean (SD) change in IMT compared between the 2 groups (0.014 [0.046] mm) was significant (P=.02). Also, pravastatin significantly reduced mean low-density lipoprotein cholesterol levels compared with placebo (−24.1% vs +0.3%, respectively; P<.001). No differences were observed for growth, muscle or liver enzymes, endocrine function parameters, Tanner staging scores, onset of menses, or testicular volume between the 2 groups.

Conclusion Two years of pravastatin therapy induced a significant regression of carotid atherosclerosis in children with familial hypercholesterolemia, with no adverse effects on growth, sexual maturation, hormone levels, or liver or muscle tissue.
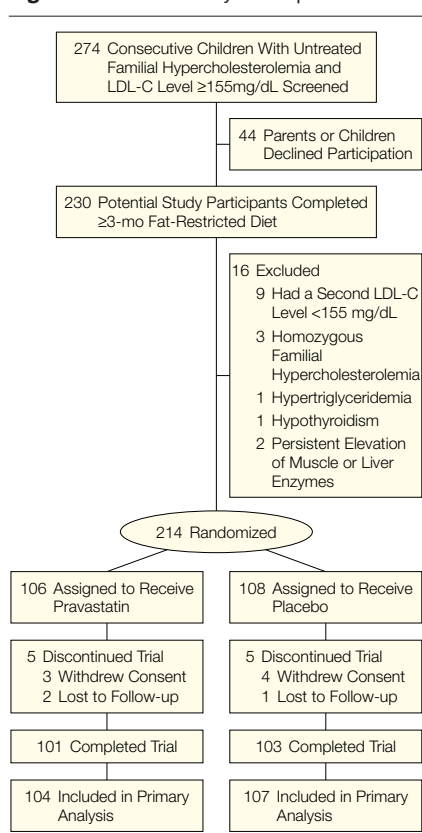*JAMA. 2004;292:331-337*   www.jama.com

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Figure 1. Flow of Study Participants

274 Consecutive Children With Untreated Familial Hypercholesterolemia and LDL-C Level ≥155mg/dL Screened

44 Parents or Children Declined Participation

230 Potential Study Participants Completed ≥3-mo Fat-Restricted Diet

16 Excluded
  9 Had a Second LDL-C Level <155 mg/dL
  3 Homozygous Familial Hypercholesterolemia
  1 Hypertriglyceridemia
  1 Hypothyroidism
  2 Persistent Elevation of Muscle or Liver Enzymes

214 Randomized

106 Assigned to Receive Pravastatin

108 Assigned to Receive Placebo

5 Discontinued Trial
  3 Withdrew Consent
  2 Lost to Follow-up

5 Discontinued Trial
  4 Withdrew Consent
  1 Lost to Follow-up

101 Completed Trial

103 Completed Trial

104 Included in Primary Analysis

107 Included in Primary Analysis

LDL-C indicates low-density lipoprotein cholesterol.

arterial wall thickness and, finally, to clinically important coronary stenoses, often in a span of less than 3 decades.

On diagnosis, adult familial hypercholesterolemia patients are prescribed lifelong treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), but postponing statin treatment until adulthood might allow development of significant arterial lesions in young familial hypercholesterolemia patients. Accordingly, early initiation of statin treatment in children with familial hypercholesterolemia might be advantageous, but unfortunately, studies of such treatment have so far only addressed short-term tolerability and safety.[12-16]

Given the effects of statins on endogenous cholesterol biosynthesis, growth and sexual development might be 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 children with familial hypercholesterolemia; we used carotid IMT to measure efficacy and growth and maturation to assess the safety of long-term exposure. 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.[17-19]

METHODS

Study Design and Participants

The study was a prospective, randomized, double-blind, placebo-controlled trial in children with heterozygous familial hypercholesterolemia (**FIGURE 1**). The study recruited children between December 7, 1997, and October 4, 1999, at the Academic Medical Center, University of Amsterdam, the Netherlands, and followed them up for 2 years; the last patient left the study on November 4, 2001. Children were eligible when they met the following criteria: 1 parent with a definite clinical or molecular diagnosis of familial hypercholesterolemia; age between 8 and 18 years; after 3 months on fat-restricted diet, 2 fasting samples with LDL-C levels of at least 155 mg/dL (4.0 mmol/L) (99.6% chance of having an LDL receptor mutation[20]) and triglyceride levels below 350 mg/dL (4.0 mmol/L); adequate contraception use in sexually active girls; and no drug treatment for familial hypercholesterolemia or use of plant sterols. Reasons for exclusion were homozygous familial hypercholesterolemia, hypothyroidism, and abnormal levels of muscle or liver enzymes. The institutional review board at the Academic Medical Center approved the study protocol. Written informed consent was obtained from all children and their parents.

All children were instructed to continue a fat-restricted diet and to maintain habitual physical activity during the trial. Seven-day diet histories were obtained 18 months into the treat-ment period. Completed menu checklists were analyzed by a dietitian and compared with Dutch advice standards for children and adolescents[21] and a survey of Dutch children's and adolescents' habits.[22]

Consenting children with familial hypercholesterolemia were randomly assigned to receive either pravastatin or placebo. Randomization was achieved by a computer-generated sequence in blocks of 8 participants. Children younger than 14 years of age received half a tablet (equivalent to pravastatin, 20 mg, in the intervention group), whereas those aged 14 years or older received 1 tablet (pravastatin, 40 mg) daily in the evening. Placebo tablets resembled pravastatin. Study drug compliance was monitored by tablet counting. Children were evaluated every 6 months for 2 years by a single physician masked to group assignment.

Primary Efficacy Outcome

The primary efficacy outcome of this study was defined as the change from baseline in mean carotid IMT compared between the pravastatin and placebo groups at 2 years of follow-up. Mean carotid IMT was defined as the mean IMT of the right and left common carotid, the carotid bulb, and the internal carotid far wall segments. 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, the mean carotid IMT was also considered missing.

One experienced sonographer (blinded) performed all B-mode ultrasound examinations. B-mode ultrasound image acquisition for the IMT measurements was performed at entry and after 1 and 2 years of follow-up. An Acuson 128XP/10v (Acuson Corp, Mountain View, Calif) ultrasound instrument equipped with a 5-10 MHz L7 (Acuson L7) and Extended Frequency ultrasound system software,

version 7.02 (Acuson Corp) was used. The left and right far walls of the carotid artery segments were imaged in a standardized magnification (2×2 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). At the end of the study, 1 image analyst (blinded) batch-read all ultrasound images in a random fashion regarding both participants and the order of their ultrasound visits. In-house–designed software (eTrack, version 2.3, W. J. Stok, Department of Physiology, Academic Medical Center, University of Amsterdam) was used as previously published.[23]

Lipids and Lipoproteins

Blood samples for measurement of lipids and lipoproteins were collected after at least a 12-hour overnight fast at baseline, 3-month intervals for the first year, and 6-month intervals the second year. Plasma total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined with the use of commercially available kits (Boehringer, Mannheim, Germany). Levels of LDL-C were calculated using the Friedewald equation.[24] Lipoprotein(a) concentrations were determined with the use of the Apo-Tek enzyme-linked immunosorbent assay (Organon Teknika, Durham, NC). Mutations in the LDL receptor gene were detected as previously described.[25]

Primary Safety Outcome

To measure deleterious effects on maturation and/or growth, we measured the levels of sex steroids, gonadotropins, and variables of the pituitary-adrenal axis at baseline and at 1 and 2 years. Measurements of children's height, weight, body surface area,[26] Tanner staging (genitals/breasts, pubic and axillary hair), and menarche or testicular volume were also obtained at the same time points. Body mass index was calculated as weight in kilograms divided by the square of height in meters. School records were reviewed for education level and yearly progress. To

detect potential adverse effects on muscle and liver enzymes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine phosphokinase (CPK) were assessed at the same time as lipids.

Sample Size Calculation

Primary Efficacy Outcome. The sample size for this study was based on the primary efficacy outcome, change from baseline to 2-year follow-up in mean carotid IMT compared between the 2 groups. Prior to the trial, replicate ultrasound measurements were performed in 20 children with familial hypercholesterolemia 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 (the σ of the mean for children with familial hypercholesterolemia and that of their siblings were similar). A sample size, N, for an effect size, Δ, and the σ were calculated according to $N = 2[(Z\alpha + Z\beta)\sigma/\Delta]^2$. We set the 2-sided α (type I error) at .05 and the β (type II error) at .10 (power of 90%). Based on these assumptions, a sample size of approximately 100 children in each group was needed to detect a difference of 0.02 mm in mean carotid IMT over a 2-year period.

Primary Safety Outcome. We subsequently used this sample size to calculate which safety outcome differences could be detected. Height measurements were first transformed to standard deviation scores (SDS) using the Dutch Child Growth Foundation's growth reference program (Growth Analyzer 2.0 SP2, version 2.2) to adjust for age and sex. For example, an SDS of 0 means that the measurement of the individual is equal to the mean of the reference population of the same age and sex. We calculated the difference between the SDS at the start of the study and the SDS after 2 years of follow-up for each child. The sample size of 100 in each group had 90% power to detect a difference of 0.18 SDS (SD, 0.40) with a 2-sided significance level of .05. Two expert pediat-

ric endocrinologists considered a difference of 0.25 SDS to be clinically relevant.

The sample size of 50 boys in each group had 90% power to detect a probability of 0.68 that a measurement of testicular volume in the pravastatin group is less than an observation in the placebo group with a 2-sided significance level of .05. The pediatric endocrinologists considered a probability of 0.7 to be clinically relevant. The power for other safety outcomes was not calculated.

Statistical Analyses

At baseline, mean values between the treatment groups were compared using a *t* test; data with a skewed distribution were first log-transformed. χ^2 Tests were applied for comparing distributions of dichotomous data between the groups. Differences in IMT between the treatment groups in terms of change from baseline after 2 years 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 effects of age, sex, and interaction terms. In some cases, more than 1 child per family was included, and consequently, data were related to a small extent. Therefore, data were also analyzed with linear regression analysis adjusted for family number using generalized estimating equations in the GENMOD procedure of SAS. Treatment differences in change from baseline after 2 years in terms of lipids, lipoproteins, and safety measurements (hormones, liver and muscle enzymes, height, weight, and menarche or testicular volume) were analyzed with ANCOVA, with adjustments made for baseline values. Data with a skewed distribution were first log-transformed. Occurrences of moderate elevations of AST, ALT, and CPK during 2 years of treatment were compared by using the Fisher exact test. Furthermore, mixed-model analysis of variance with (linear) time and treatment effects and their interactions were used

to assess the rates of change in AST, ALT, and CPK during follow-up.

Analyses were interpreted at the 2-sided significance level of .05. Statistical analyses were computed with SAS software, version 8.02 (SAS Institute Inc, Cary, NC).

RESULTS
Characteristics of Children

In total, 274 consecutive statin-naive children whose initial LDL-C levels were at least 155 mg/dL were evaluated (Figure 1). In 44 cases, parents, child, or both declined participation, and in 9 children, the second LDL-C level was below 155 mg/dL. Seven children were excluded for homozygous familial hypercholesterolemia (n=3), hypothyroidism (n=1), hypertriglyceridemia (n=1), or persis-

tently 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 (Figure 1). The mean and median age was 13.0 years (range, 8.0-18.5 years). In 205 children (96%), the diagnosis of familial hypercholesterolemia was confirmed by characterization of the mutation in the LDL receptor gene. Baseline characteristics were similar in the 2 groups with respect to age, smoking frequency, systolic and diastolic blood pressure, sex distribution, and, in girls, menarche (TABLE 1). Premature cardiovascular disease was present in 34% of the affected parents (median age, 37 [range, 20-50] years), while 10% of parents with familial hypercholesterolemia had already died of cardiovascular disease (median age, 37 [range, 23-45] years).

Ten children (all girls; 5 in the pravastatin and 5 in the placebo group) discontinued the study prematurely because they withdrew consent. However, only 3 of them had no 2-year follow-up data (2 children in the pravastatin group and 1 in the placebo group). The available lipids, IMT, and safety data were included in the primary efficacy and safety analyses as collected until discontinuation. At 18 months of treatment, both groups were compliant with their diets, with better fat intake than found in the survey of habits[22] and slightly worse fat intake than the recommended levels.[21] The recommended intake of total fat for ado-

lescents in the Netherlands is 30%, 10% as saturated fat. The surveyed Dutch adolescents ate 35% total fat and 15% saturated fat, whereas our study cohort ingested 32.6% total fat and 12.1% saturated fat.

Primary Efficacy Outcome

At baseline, the means of the separate carotid IMT segments as well as the combined carotid IMT were similar in the pravastatin and placebo groups (TABLE 2). At the end of the 2-year trial, all of the carotid arterial wall segments showed a trend toward attenuation of IMT in the pravastatin group, while these segments exhibited a trend toward IMT increase in the placebo group (FIGURE 2). Hence, the mean combined carotid IMT was attenuated after 2 years of treatment with pravastatin (mean [SD] change in IMT, −0.010 [0.048] mm; P=.049) compared with a trend toward increase of the mean carotid IMT in the placebo group (mean [SD] change in IMT, +0.005 [0.044] mm; P=.28) (Table 2). The overall change in carotid IMT (0.014 [0.046] mm) differed significantly between the 2 groups (P=.02). Multivariate analyses showed that neither sex nor age significantly influenced these results (mean [SD] change in IMT, 0.010 [0.066] mm; P value changed from .02 to .03). When the results were analyzed using generalized estimating equations, the overall results differed only marginally from the ANCOVA analysis, but the difference in changes for the common carotid artery segment be-

Table 1. Baseline Characteristics of Participants*

	Pravastatin (n = 106)	Placebo (n = 108)
Age, y	13.0 (3.0)	13.0 (2.9)
Younger than 14 y, No. (%)	65 (61)	63 (58)
Girls, No. (%)	57 (54)	57 (53)
Premenarche (girls), No. (%)	26 (46)	20 (35)
Smokers, No. (%)	11 (10)	13 (12)
Weight, kg	49.1 (15.5)	49.7 (14.7)
Height, cm	156 (16)	157 (13)
Height SDS	0.2 (1.1)	0.2 (0.9)
BMI	20 (3)	20 (4)
BSA, m²	1.4 (0.3)	1.4 (0.3)
Blood pressure, mm Hg		
Systolic	111 (13)	110 (12)
Diastolic	61 (9)	62 (9)
Pulse, beats/min	72 (13)	72 (11)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; BSA, body surface area; SDS, standard deviation score.
*Data are expressed as mean (SD) unless otherwise noted.

Table 2. Mean Changes From Baseline in IMT of Carotid Artery Segments and Lipids and Lipoproteins at 2-Year Follow-up*

	Baseline		Change From Baseline		
	Pravastatin (n = 106)	Placebo (n = 108)	Pravastatin (n = 104)	Placebo (n = 107)	P Value†
Carotid IMT, mm‡	0.497 (0.055)	0.492 (0.045)	−0.010 (0.048)	0.005 (0.044)	.02
Lipids, mg/dL					
Total cholesterol	302 (56)	300 (47)	−56 (43)	2 (39)	<.001
LDL cholesterol	239 (53)	237 (46)	−57 (40)	0 (36)	<.001
HDL cholesterol	47 (10)	48 (11)	3 (10)	1 (9)	.09
Triglycerides	70 (50 to 112)	64 (46 to 90)	−12 (−35 to 16)	1 (−20 to 22)	.21
Lipoprotein(a), g/L	0.13 (0.06 to 0.32)	0.12 (0.04 to 0.24)	0.01 (−0.00 to 0.05)	0.00 (−0.01 to 0.03)	.09

Abbreviations: HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein.
SI conversions: To convert cholesterol values to mmol/L, divide by 38.67; to convert triglyceride values to mmol/L, divide by 88.57.
*Data are expressed as mean (SD) except triglycerides and lipoprotein(a), expressed as median (interquartile range).
†P values apply to the difference in change from baseline between the 2 groups.
‡Mean carotid IMT was calculated as the means of common carotid artery, carotid bulb, and internal carotid artery.

tween the 2 groups became statistically significant (*P* value changed from .06 to .04). The difference in the changes in the mean combined carotid IMT became statistically slightly more pronounced (*P* value changed from .02 to .01).

Lipid and Lipoprotein Levels

As expected, pravastatin significantly reduced mean LDL-C levels compared with placebo (−24.1% vs +0.3%; *P*<.001; absolute differences are shown in Table 2), which was maintained over the 2-year study period. High-density lipoprotein cholesterol, triglyceride, and lipoprotein(a) levels did not change significantly in pravastatin-treated children.

Safety and Tolerability

Compliance with study medication, as assessed by tablet counting, revealed that 84% of tablets were taken, whereas the mean visit attendance per child was 95% of all study visits.

At baseline, the education level in the 2 groups was equal (*P*=.68). During the

2-year treatment, pravastatin had no effect on academic performance; in both groups, 11 children had to repeat a school year once.

The height of the children increased similarly in the pravastatin and the placebo groups (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. Therefore, body mass index increased 1.3 (1.6) in the pravastatin group and 1.2 (1.3) in the placebo group. During the trial, 5 girls in the placebo group started menses at a mean age of 12.3 (1.3) years, whereas 12 girls in the pravastatin group started menses at a mean age of 12.4 (1.8) years. At the end of the trial, in both groups, 42 of 57 girls were postmenarchal. During the 2 years of follow-up, changes in testicular volume and Tanner staging scores were not different between the groups (**TABLE 3** and **TABLE 4**).

All endocrine function parameters at entry and after 2 years were not significantly different between the pravastatin

and placebo groups (Table 3). At the end of the trial, no relevant differences were observed with respect to changes from

Figure 2. Mean IMT Changes From Baseline for the Different Carotid Arterial Wall Segments in the Pravastatin and Placebo Groups
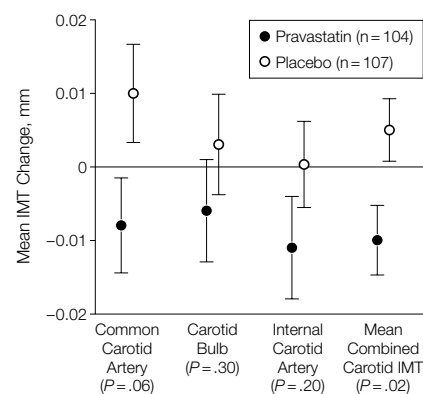
IMT indicates intima-media thickness. Error bars indicates SE. *P* values for the difference between the 2 groups in change from baseline were calculated using analysis of covariance adjusted for baseline values.

Table 3. Safety Measurements at Baseline and at 2 Years of Follow-up

	Baseline		Change From Baseline		
	Pravastatin (n = 106)	Placebo (n = 108)	Pravastatin (n = 104)	Placebo (n = 107)	*P* Value
Physical characteristics					
Weight, kg*	49.1 (15.5)	49.7 (14.7)	8.0 (5.8)	7.8 (5.5)	.83
Height, cm*	156 (16)	157 (13)	7.9 (5.7)	7.8 (6.1)	.94
Height SDS*	0.2 (1.1)	0.2 (0.9)	−0.01 (0.38)	−0.01 (0.46)	.87
BMI*	20 (3)	20 (4)	1.3 (1.6)	1.2 (1.3)	.58
BSA, m²*	1.4 (0.3)	1.4 (0.3)	0.2 (0.1)	0.2 (0.1)	.87
Testis volume (boys), mL†	4 (2 to 14)	4 (3 to 16)	2 (1 to 14)	3 (2 to 7)	.95
Liver and muscle enzymes, U/L†					
AST	21 (16 to 27)	22 (17 to 26)	2 (−2 to 5)	2 (−2 to 5)	.24
ALT	13 (12 to 18)	14 (11 to 18)	0 (−4 to 4)	0 (−5 to 4)	.18
CPK	100 (77 to 144)	102 (75 to 145)	−4 (−20 to 11)	−3 (−22 to 20)	.68
Hormones†					
Corticotropin, ng/L	28 (18 to 39)	27 (20 to 40)	1 (−9 to 11)	0 (−7 to 6)	.42
Cortisol, nmol/L	240 (180 to 340)	240 (190 to 310)	−10 (−70 to 60)	10 (−60 to 110)	.13
DHEA-S, µmol/L	2.4 (1.5 to 3.7)	2.9 (1.8 to 4.8)	0.6 (0.0 to 1.4)	0.7 (−0.1 to 1.5)	.46
FSH, U/L	1.7 (0.6 to 3.8)	1.8 (1.0 to 3.6)	0.2 (−0.5 to 1.4)	0.4 (−0.8 to 1.8)	.74
LH, U/L	1.1 (0.5 to 3.3)	0.5 (0.5 to 3.5)	0.2 (0.0 to 1.7)	0.1 (0.0 to 1.3)	.34
Thyrotropin, mU/L	2.1 (1.3 to 2.7)	2.0 (1.5 to 2.8)	−0.3 (−0.7 to 0.4)	−0.1 (−0.7 to 0.4)	.86
17b-Estradiol (girls), nmol/L	0.05 (0.05 to 0.14)	0.05 (0.05 to 0.16)	0 (−0.01 to 0.09)	0 (−0.07 to 0.09)	>.99
Testosterone (boys), nmol/L	1.4 (0.4 to 16.0)	2.3 (0.4 to 17.5)	4.1 (0.0 to 11.3)	2.4 (0.0 to 8.9)	.68

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; BSA, body surface area; CPK, creatine phosphokinase; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SDS, standard deviation score.
SI conversion: To convert testosterone to ng/dL, divide by 0.0347.
*Data are expressed as mean (SD).
†Data are expressed as median (interquartile range) because of skewed distribution.

Table 4. Tanner Stage Changes From Baseline to 2-Year Follow-up

	Treatment Group, No. (%)		Between-Group P Value
	Pravastatin	Placebo	
Girls			
No change in stage	19 (35)	22 (39)	.61
Changed ≥1 stage	36 (65)	34 (61)	
Boys			
No change in stage	22 (45)	17 (33)	.24
Changed ≥1 stage	27 (55)	34 (67)	
All			
No change in stage	41 (39)	39 (36)	.66
Changed ≥1 stage	63 (61)	68 (64)	

baseline for AST, ALT, or CPK (Table 3). No higher than 3-fold elevation occurred in ALT and elevation of higher than 3-fold AST levels occurred only twice in the placebo group. A higher than 4-fold elevation in CPK occurred 4 times in the pravastatin group and 3 times in the placebo group. There was no difference between the 2 groups with respect to the rate of change of AST, ALT, 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 1 week after stopping the study regimen, her CPK level decreased to normal levels. The study regimen was reinstated, and at the end of the trial, the child was found to have been allocated to placebo.

COMMENT

In this randomized, double-blind, placebo-controlled study, we assessed the 2-year efficacy and safety of pravastatin therapy in children with familial hypercholesterolemia. We were able to show that statin treatment improved the lipoprotein profile toward more physiological levels and we observed regression of carotid IMT. This shows that the increased arterial wall thickness progression found in children with familial hypercholesterolemia is reversible. Moreover, we extensively analyzed possible adverse events and untoward influences on growth and maturation of the children and none were observed, although some of our safety outcomes may have been underpowered. Finally, the long-term tolerability of pravastatin was excellent in these children. Discontinu-

ation of the study protocol was a rare event and equally distributed between the active medication and placebo groups. So far, only a few studies have evaluated statin treatment in children with familial hypercholesterolemia.[12-16] These studies showed promising short-term efficacy and reassuring safety in terms of changes in hepatic and muscle enzymes. Our results are based on longer follow-up and broader safety measurements. While a previous study using simvastatin did show mild changes with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition,[15] our study showed that levels of dehydroepiandrosterone sulfate and cortisol were unchanged after 2 years of pravastatin therapy.

Several methodological aspects of our study require comment. Carotid IMT progression in the placebo group was less than expected, possibly as a consequence of strict adherence to a healthy lifestyle, including a strict diet, frequent physical activity, and a low frequency of cigarette smoking. Also, we used only a surrogate marker of future vascular disease and could not assess clinical end points, but solid evidence exists that changes in arterial wall IMT are predictive of cardiovascular outcome.[17-19] To limit IMT measurement variability, a single ultrasound machine was used, 1 experienced sonographer performed all ultrasonagraphy, and images were analyzed by a single reader. To reduce variability further, image analysis software automatically investigated each IMT measurement and accounted for the video line interpola-

tion of the ultrasound equipment. In addition, the double-blind design ensured that all study personnel were unaware of treatment allocation. Nevertheless, our findings cannot be extrapolated to children with an increased atherosclerotic risk as a result of disorders other than familial hypercholesterolemia. In children with familial hypercholesterolemia, 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 cardiovascular disease. Our IMT findings and the observed efficacy of pravastatin treatment should therefore be restricted to children with familial hypercholesterolemia.

Although this trial in children with familial hypercholesterolemia has, to our knowledge, the most extensive follow-up to date, data on even longer-term safety and efficacy of statin therapy in children are needed.

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> If we value the pursuit of knowledge, we must be free to follow wherever that search may lead us. The free mind is not a barking dog, to be tethered on a ten-foot chain.
> —Adlai E. Stevenson, Jr (1900-1965)