Efficacy and Safety of Statin Therapy in Children With Familial Hypercholesterolemia

A Randomized, Double-Blind, Placebo-Controlled Trial With Simvastatin

Saskia de Jongh, MD; Leiv Ose, MD; Tamás Szamosi, MD, PhD; Claude Gagné, MD; M. Lambert, MD; Russell Scott, MD; P. Perron, MD; Dries Dobbelrae, MD; M. Saborio, MD; Mary B. Tuohy, RN; Michael Stepavanage, MS; Aditi Sapre, PhD; Barry Gumbiner, MD; Michele Mercuri, MD, PhD; A.S. Paul van Trotsenburg, MD; Henk D. Bakker, MD, PhD; John J.P. Kastelein, MD, PhD; for the Simvastatin in Children Study Group

Background—A multicenter, randomized, double-blind, placebo-controlled study was conducted to evaluate LDL cholesterol-lowering efficacy, overall safety, and tolerability and the influence on growth and pubertal development of simvastatin in a large cohort of boys and girls with heterozygous familial hypercholesterolemia (heFH).

Methods and Results—A total of 173 heFH children (98 boys and 75 girls) were included in this study. After a 4-week diet/placebo run-in period, children with heFH were randomized to either simvastatin or placebo in a ratio of 3:2. Simvastatin was started at 10 mg/d and titrated at 8-week intervals to 20 and then 40 mg/d. During a 24-week extension period, the patients continued to receive simvastatin (40 mg) or placebo according to their assignment. After 48 weeks of simvastatin therapy, there were significant reductions of LDL cholesterol (−41%), total cholesterol (−31%), apolipoprotein B (−34%), VLDL cholesterol (−21%), and triglyceride (−9%) levels. HDL cholesterol and apolipoprotein A-I levels were increased by 3.3% and 10.4%, respectively (not significant). No safety issues became evident. Except for small decreases in dehydroepiandrosterone sulfate compared with placebo, there were no significant changes from baseline in adrenal, gonadal, and pituitary hormones in either treatment group.

Conclusions—Simvastatin significantly reduced LDL cholesterol, total cholesterol, triglyceride, VLDL cholesterol, and apolipoprotein B levels and was well tolerated in children with heFH. There was no evidence of any adverse effect of simvastatin on growth and pubertal development. Therefore, simvastatin at doses up to 40 mg is a well-tolerated and effective therapy for heFH children. (Circulation. 2002;106:2231-2237.)

Key Words: cholesterol ■ drugs ■ hypercholesterolemia ■ lipids ■ pediatrics

Heterozygous familial hypercholesterolemia (heFH) is a frequent, inherited disorder of lipoprotein metabolism caused by mutations in the LDL receptor gene. Consequently, patients show symptoms of coronary heart disease (CHD) at a young age. In men with untreated heFH, this risk of CHD is ≈50% by the age of 50 years.

In heFH children, the disease is mostly asymptomatic. However, even in the general population, autopsy reports of healthy children show atherosclerotic lesions at a young age. In view of the aggressive nature of vascular disease in young adult heFH patients, we can assume that these atherosclerotic changes begin in early childhood. Morphological and functional changes of the arteries can predict future CHD and are present in hypercholesterolemic children, underscoring the importance of aggressive and early treatment of dyslipidemia to prevent premature events in heFH.

The recommended therapy for heFH children consists of dietary intervention, but the long-term efficacy of such therapy in children is very poor. The US National Cholesterol Education Program (NCEP) recommends drug therapy for children aged >10 years whose LDL cholesterol (LDL-C) remains elevated after dietary therapy. Bile acid sequestrants are
considered the drugs of choice, but the lipid-lowering efficacy is modest, and long-term compliance remains poor.13,14

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are effective, safe, and well-tolerated lipid-altering agents that have been proven to significantly reduce the incidence of CHD, stroke, and peripheral vascular disease in adults.15,16 Thus far, there have only been a few studies evaluating statins in children,17–23 but these studies were either not randomized or controlled, they included only boys, they had a modest sample size, or they were of short duration. The present study was designed to evaluate the LDL-C–lowering efficacy of simvastatin in a large cohort of both boys and girls with heFH to determine the overall safety and tolerability of simvastatin and to assess the influence of simvastatin on growth and pubertal development.

Methods

Study Design
This was an international multicenter (n=9), double-blind, randomized, parallel study of 173 pediatric heFH patients.24 Entry criteria included children aged 10 to 17 years with LDL-C levels between 4.1 and 10.3 mmol/L and 1 parent with a confirmed diagnosis of heFH. Children with homozygous familial hypercholesterolemia and secondary hyperlipidemia were excluded. Boys were in Tanner stage II or above, and girls were postmenarchal for at least 1 year before the initiation of the present study. The Institutional Review Boards of the participating centers approved the protocol, and written informed consent was obtained from all children and parents.

After a 4-week diet/placebo run-in period, children were randomized to active treatment or matching placebo in a ratio of 3:2 and stratified by sex. Simvastatin was started at 10 mg/d and was increased at 8-week intervals to 20 and then 40 mg/d for the remainder of the study (period 1) and for the 24-week extension (period 2). Visits were every 4 weeks. The menstrual cycle was monitored throughout the study period by recording the first day of the menstrual flow. Tanner staging based on testicle size (boys) and breast size (girls) was used for pubertal development.25,26

Laboratory Methods

Efficacy measurements (total cholesterol [total-C], triglycerides [TGs], LDL-C, and HDL cholesterol [HDL-C]) and safety measurements (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and creatine phosphokinase [CK]) were performed at every visit or every other visit (apolipoprotein B [apoB] and apoA-I).

Discontinuation criteria included persistent >3-fold the upper limit of normal (ULN) increases in ALT or AST and >10-fold the ULN for CK with or without muscular symptoms or 5- to 10-fold increases in CK with symptoms. Adrenal hormones (cortisol and dehydroepiandrosterone sulfate [DHEAS]), gonadal hormones (estradiol for girls and testosterone for boys), and pituitary hormones (lutropin [LH] and follicle-stimulating hormone [FSH]) were also assessed at regular intervals. In girls, β-human choric gonadotropin was measured at every visit.

Samples for serum chemistry, hematology, urinalysis, and hormones were analyzed by Medical Research Laboratories or Clinical Research Laboratories. Throughout the present study, the laboratories participated in and remained certified by the National Heart, Lung, and Blood Institute, Centers for Disease Control Part III program.27 Total-C, TGs, and HDL were analyzed as previously described.28–29 FSH, LH, estradiol, DHEAS, and testosterone were measured by competitive radioimunoassay with the use of reagent kits from Diagnostic Products Corp, and cortisol was measured by a fluorescence polarization immunoassay on an Abbott TDX analyzer.

Statistical Analysis

Data were analyzed by an intention-to-treat approach; ie, all patients who had a baseline measurement and at least 1 postdrug measurement were included in the analysis. Parametric (or appropriate...
Results

Patients and Baseline Characteristics

Of 223 children screened for eligibility, a total of 175 children were included in the present study: 69 were randomized to placebo, and 106 were randomized to simvastatin (Figure 1). Two children in the placebo group were excluded from the intention-to-treat analysis because of loss of follow-up and withdrawal of consent. The majority of randomized children were boys (52% of the placebo group, 59% of the simvastatin group; Table 1). At baseline, the 2 treatment groups were similar regarding demographic characteristics, lipids, and lipoproteins.

Mean total-C and LDL-C were severely elevated in both groups, as can be expected in heFH.

Efficacy of Simvastatin

Mean percent changes from baseline for lipids, lipoproteins, and C-reactive protein (hsCRP) are shown in Table 2 (all time points) and Figure 2 (week 48). Compared with placebo, simvastatin produced significant (P<0.001) reductions in LDL-C at all time points. At 24 weeks, LDL-C levels were reduced 38.4% (from 5.28 mmol/L at baseline to 3.24 mmol/L in the simvastatin group) compared with a 1.2% reduction in the placebo group (P<0.001 between groups). Similarly, simvastatin reduced LDL-C by 40.7% (from 5.28 mmol/L at baseline to 3.11 mmol/L at week 48) compared with a 0.3% increase in the placebo group (P<0.001). Total-C, VLDL cholesterol (VLDL-C), and apoB were also significantly (P<0.001) reduced relative to placebo at all time points. Significant reductions in TGs were seen at weeks 8, 16, and 48. HDL-C and apoA-I were increased for all weeks; however, these increases were only significant

TABLE 2. Mean Percent Change From Baseline for Lipids and Lipoproteins During 48 Weeks of Simvastatin Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Simvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 1</td>
<td>Period 2</td>
<td>Period 1</td>
</tr>
<tr>
<td>Total-C, %</td>
<td>-23.9±8.5*</td>
<td>-28.3±11.5*</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>-31.4±10.5*</td>
<td>-38.4±16.0*</td>
</tr>
<tr>
<td>VLDL-C, %</td>
<td>-11.8</td>
<td>-12.5</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>4.7±12.6</td>
<td>4.9±13.5</td>
</tr>
<tr>
<td>TGs, %</td>
<td>-8.9</td>
<td>-7.9</td>
</tr>
<tr>
<td>ApoA-I, %</td>
<td>5.4±12.4</td>
<td>7.2±14.2</td>
</tr>
<tr>
<td>ApoB, %</td>
<td>-28.8±8.8*</td>
<td>-34.1±13.5*</td>
</tr>
<tr>
<td>hsCRP, %</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

All values are given as mean±SD percent change from baseline, except for VLDL-C, TGs, and hsCRP, which are given as median (range) percent change from baseline.

*P<0.001 vs placebo; †P<0.05 vs placebo.

---

Figure 2. Effect of 48 weeks of simvastatin (40 mg) or placebo therapy on lipids and lipoproteins of heFH children.
TABLE 3. Clinical and Laboratory AEs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Period 1 (24 wk)</th>
<th>Period 2 (48 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simvastatin (n=106)</td>
<td>Placebo (n=109)</td>
</tr>
<tr>
<td></td>
<td>Simvastatin (n=86)</td>
<td>Placebo (n=88)</td>
</tr>
<tr>
<td>Drug-related clinical AEs*</td>
<td>6 (5.7%)</td>
<td>3 (4.3%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (1.9)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Cold sore</td>
<td>0 (1.4)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Drug-related laboratory AEs*</td>
<td>2 (1.9)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>2 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>2 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Increased CK</td>
<td>0 (1.5)</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

Values are n (%). CK indicates creatine phosphokinase.

A patient may have 2 or more AEs; the patient is only counted once in a category.

None of the differences between the placebo and simvastatin groups in either period 1 or 2 reached statistical significance.

* Determined by the investigator to be possibly, probably, or definitely drug related.

relative to placebo at week 24 (P<0.05). No changes from baseline in hscrP were observed in either treatment group at week 24 or 48.

Safety

Of the 175 children randomized in period 1, 6 (5.7%) of the 106 children in the simvastatin group compared with 3 (4.3%) of the 69 children in the placebo group reported ≥1 drug-related clinical adverse event (AE) (Table 3). There were no serious AEs (life-threatening, causing disability, or requiring hospitalization), and the only discontinuation was a child on simvastatin (10 mg) who developed infectious mononucleosis (not drug-related). Of the 144 children who started period 2, 4 (4.7%) of the children in the simvastatin group compared with 2 (3.4%) in the placebo group reported ≥1 drug-related clinical AE. None of the differences between the placebo and simvastatin groups during periods 1 and 2 reached statistical significance (Table 3).

One or more laboratory AEs were reported by 9 children, 6 (5.7%) on simvastatin and 3 (4.5%) on placebo, during period 1, and by 5 children, 4 (4.7%) on simvastatin and 1 (1.7%) on placebo, during period 2. No serious laboratory AEs were reported, and none of the children discontinued the study because of laboratory AEs (Table 3). Two children on simvastatin had single >3-fold ULN increases in AST and/or ALT. In 1 case, which was considered drug-related but not clinically significant by the investigator, a child experienced several (<3-fold ULN) elevations during the extension as well as one >3-fold increase. Therapy was interrupted for a 10-day period, and the child’s levels returned to normal while still on the study drug. This patient discontinued the study at week 41 because of inadvertent unblinding by the investigator. The other occurred in the child with infectious mononucleosis. One child on simvastatin who had concomitant administration of erythromycin experienced an increase in CK (>10-fold ULN) without muscle symptoms, which returned to normal after completion of the antibiotics. Two children on simvastatin had an increase in CK (>5-fold ULN). In both cases, CK levels returned to normal in repeat tests, and the patients completed the study.

Growth and Sexual Maturation

Baseline and absolute change from baseline values for parameters related to growth and sexual maturation during both
significant TG reductions were also seen in the present study, relative to placebo, simvastatin therapy produced large, clinically significant reductions in total-C, LDL-C, VLDL-C, TGs, and apoB above the 95th percentile for age and sex.30 The children had baseline levels of total-C, LDL-C, VLDL-C, TGs, and apoB above the 95th percentile for age and sex.30

The results of this trial demonstrate that simvastatin beneficially modified the lipid/lipoprotein profile of boys and girls with heFH. Furthermore, simvastatin was well tolerated and had no deleterious effects on growth or pubertal development. Confirming that simvastatin is an effective lipid-lowering agent in children and adolescents with heFH.

Safety
There was no evidence of safety issues during the present study. There were no cases of myopathy, and no significant differences were observed between the treatment groups regarding the number of clinical and laboratory AEs, drug-related AEs, or clinically meaningful elevations in hepatic transaminases (ALT and AST) and creatine phosphokinase.

Growth and Sexual Maturation
Development as measured by clinical growth and Tanner staging was normal in the active treatment group, and no significant differences between treatment groups were observed regarding change from baseline in either testicular volume or menstrual cycle length. Because cholesterol is a precursor of the adrenal hormones, cortisol and DHEAS, and the gonadal hormones, testosterone and estradiol, inhibiting the rate-limiting enzyme (3-hydroxy-3-methylglutaryl coenzyme A reductase) in cholesterol synthesis could have resulted in decreased production of these hormones. No differences were evident regarding the change from baseline for cortisol; however, DHEAS levels were significantly reduced relative to placebo in both boys and girls. These absolute differences were probably too small to be of any clinical relevance, as evidenced by an absence of growth or pubertal development abnormalities. In 2 previous studies,19,23 lovastatin produced small but significant increases in DHEAS levels relative to placebo. Again, no clinical significance was attributed to these effects on DHEAS. In the present study, there were no significant changes from baseline. These findings are consistent with the data from studies evaluating the effect of long-term statin therapy on gonadal and adrenal steroid production in adults.32,33 The hypothalamic feedback factors (LH and FSH) for the gonadal hormones were normal in the active treatment group, and no significant differences between treatment groups were observed regarding change from baseline in either testicular volume or menstrual cycle length. Because cholesterol is a precursor of the adrenal hormones, cortisol and DHEAS, and the gonadal hormones, testosterone and estradiol, inhibiting the rate-limiting enzyme (3-hydroxy-3-methylglutaryl coenzyme A reductase) in cholesterol synthesis could have resulted in decreased production of these hormones. No differences were evident regarding the change from baseline for cortisol; however, DHEAS levels were significantly reduced relative to placebo in both boys and girls. These absolute differences were probably too small to be of any clinical relevance, as evidenced by an absence of growth or pubertal development abnormalities. In 2 previous studies,19,23 lovastatin produced small but significant increases in DHEAS levels relative to placebo. Again, no clinical significance was attributed to these effects on DHEAS. In the present study, there were no significant changes from baseline. These findings are consistent with the data from studies evaluating the effect of long-term statin therapy on gonadal and adrenal steroid production in adults.32,33 The hypothalamic feedback factors (LH and FSH) for the gonadal hormones were normal in the active treatment group, and no significant differences between treatment groups were observed regarding change from baseline in either testicular volume or menstrual cycle length. Because cholesterol is a precursor of the adrenal hormones, cortisol and DHEAS, and the gonadal hormones, testosterone and estradiol, inhibiting the rate-limiting enzyme (3-hydroxy-3-methylglutaryl coenzyme A reductase) in cholesterol synthesis could have resulted in decreased production of these hormones. No differences were evident regarding the change from baseline for cortisol; however, DHEAS levels were significantly reduced relative to placebo in both boys and girls. These absolute differences were probably too small to be of any clinical relevance, as evidenced by an absence of growth or pubertal development abnormalities. In 2 previous studies,19,23 lovastatin produced small but significant increases in DHEAS levels relative to placebo. Again, no clinical significance was attributed to these effects on DHEAS. In the present study, there were no significant changes from baseline. These findings are consistent with the data from studies evaluating the effect of long-term statin therapy on gonadal and adrenal steroid production in adults.32,33 The hypothalamic feedback factors (LH and FSH) for the gonadal hormones were normal in the active treatment group, and no significant differences between treatment groups were observed regarding change from baseline in either testicular volume or menstrual cycle length. Because cholesterol is a precursor of the adrenal hormones, cortisol and DHEAS, and the gonadal hormones, testosterone and estradiol, inhibiting the rate-limiting enzyme (3-hydroxy-3-methylglutaryl coenzyme A reductase) in cholesterol synthesis could have resulted in decreased production of these hormones. No differences were evident regarding the change from baseline for cortisol; however, DHEAS levels were significantly reduced relative to placebo in both boys and girls. These absolute differences were probably too small to be of any clinical relevance, as evidenced by an absence of growth or pubertal development abnormalities. In 2 previous studies,19,23 lovastatin produced small but significant increases in DHEAS levels relative to placebo. Again, no clinical significance was attributed to these effects on DHEAS. In the present study, there were no significant changes from baseline. These findings are consistent with the data from studies evaluating the effect of long-term statin therapy on gonadal and adrenal steroid production in adults.32,33 The hypothalamic feedback factors (LH and FSH) for the gonadal hormones were normal in the active treatment group, and no significant differences between treatment groups were observed regarding change from baseline in either testicular volume or menstrual cycle length. Because cholesterol is a precursor of the adrenal hormones, cortisol and DHEAS, and the gonadal hormones, testosterone and estradiol, inhibiting the rate-limiting enzyme (3-hydroxy-3-methylglutaryl coenzyme A reductase) in cholesterol synthesis could have resulted in decreased production of these hormones. No differences were evident regarding the change from baseline for cortisol; however, DHEAS levels were significantly reduced relative to placebo in both boys and girls. These absolute differences were probably too small to be of any clinical relevance, as evidenced by an absence of growth or pubertal development abnormalities. In 2 previous studies,19,23 lovastatin produced small but significant increases in DHEAS levels relative to placebo. Again, no clinical significance was attributed to these effects on DHEAS. In the present study, there were no significant changes from baseline. These findings are consistent with the data from studies evaluating the effect of long-term statin therapy on gonadal and adrenal steroid production in adults.32,33 The hypothalamic feedback factors (LH and FSH) for the gonadal hormones were normal in the active treatment group, and no significant differences between treatment groups were observed regarding change from baseline in either testicular volume or menstrual cycle length. Because cholesterol is a precursor of the adrenal hormones, cortisol and DHEAS, and the gonadal hormones, testosterone and estradiol, inhibiting the rate-limiting enzyme (3-hydroxy-3-methylglutaryl coenzyme A reductase) in cholesterol synthesis could have resulted in decreased production of these hormones. No differences were evident regarding the change from baseline for cortisol; however, DHEAS levels were significantly reduced relative to placebo in both boys and girls. These absolute differences were probably too small to be of any clinical relevance, as evidenced by an absence of growth or pubertal development abnormalities. In 2 previous studies,19,23 lovastatin produced small but significant increases in DHEAS levels relative to placebo. Again, no clinical significance was attributed to these effects on DHEAS. In the present study, there were no significant changes from baseline. These findings are consistent with the data from studies evaluating the effect of long-term statin therapy on gonadal and adrenal steroid production in adults.
have clinically meaningful effects on gonadal function in children and adolescent boys and girls.

**Statin Therapy in Children and Adolescents**

Only a few studies have been conducted to date evaluating statin therapy in children and adolescents. Stein et al. was the first to show a 40% reduction of LDL-C in the FH children treated with lovastatin or simvastatin, but that study was not controlled and involved only a small group of boys. In 1992, another small (n = 32) and uncontrolled study with simvastatin showed a 37% LDL-C reduction and excellent tolerability. Later, 3 other statin studies in children or adolescents were reported. In the first study, 72 heFH children (66% girls), aged 10 to 16 years, were randomized to placebo or pravastatin (5, 10, or 20 mg). After 12 weeks, LDL-C levels were reduced by 23%, 24%, and 33% in the groups receiving pravastatin at 5, 10, and 20 mg, respectively. Short-term safety and tolerability were excellent. The second study reported an uncontrolled study in which boys were randomized to lovastatin at 10, 20, 30, or 40 mg/d for 12 weeks. LDL-C levels were reduced by 21% to 36%, and lovastatin was again well tolerated, with no serious AEs. In the last study, 132 boys, aged 10 and 17 years, were randomized to either lovastatin or placebo. Lovastatin was started at 10 mg/d, and the dosage was doubled every 8 weeks to a maximum of 40 mg/d. Mean LDL-C levels decreased significantly relative to placebo in all active treatment groups.

Data on growth and hormonal status indicated no significant differences between lovastatin and placebo in a 48-week time period. Although these studies showed good efficacy of statins in children, they were short-term, had a limited sample size, were mostly conducted in boys, or did not provide extensive information about growth and development.

In summary, simvastatin (40 mg) was efficacious in the treatment of children and adolescents with heFH and exhibited a safety and tolerability profile similar to that seen in adults. In addition, simvastatin did not negatively influence normal growth or sexual maturation in either boys or girls. Additionally, it should be emphasized that although statin use starts in early childhood in individuals with heFH, aggressive lipid lowering is deemed necessary to prevent future CHD. Although long-term outcome data on statin use in children are not available, simvastatin might be a useful tool to optimize treatment for heFH children and adolescents, in whom the response to lifestyle intervention is often inadequate.

**Acknowledgments**

This study was supported by Merck & Co, Inc. Dr Kastelein is an established investigator of the Netherlands Heart Foundation (grant No. 2000D039). The authors thank the children and parents who participated in this study. Thanks are also extended to Laura Corsetti for project management, Dr Darbie Macaubbin for assistance with manuscript preparation, and Dr Yale Mitchel for valuable advice throughout the course of this study. Finally, we acknowledge the important contribution of the following Merck Sharp & Dohme clinical monitors: Jean-Claude Painson and Ivan Shaw (Canada), Karla Alvarado (Costa Rica), Myriam Gouttaya and Karima Boujemia (France), Cari Blom and Pauline Pasman (the Netherlands), Laszlo Veres (Hungary), Derek Siegers (New Zealand), and Kjersti Ekornrud (Norway). We thank A. Wiegman (the Netherlands) for his assistance in the patient inclusion.

**References**


Efficacy and Safety of Statin Therapy in Children With Familial Hypercholesterolemia: A Randomized, Double-Blind, Placebo-Controlled Trial With Simvastatin


for the Simvastatin in Children Study Group

Circulation. 2002;106:2231-2237
doi: 10.1161/01.CIR.0000035247.42888.82

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/17/2231

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/