Statin Treatment in Children With Familial Hypercholesterolemia
The Younger, the Better

Jessica Rodenburg, MD, PhD; Maud N. Vissers, PhD; Albert Wiegman, MD, PhD; A.S. Paul van Trotsenburg, MD, PhD; Frits A. Wijburg, MD, PhD; John J.P. Kastelein, MD, PhD; Barbara A. Hutten, PhD

Background—We previously demonstrated in a randomized placebo-controlled trial that 2-year pravastatin treatment induced a significant regression of carotid intima-media thickness (IMT) in 8- to 18-year-old children with familial hypercholesterolemia. Subsequently, we continued to follow up these children to explore the relation between the age of statin initiation and carotid IMT after follow-up on statin treatment. We also examined safety aspects of statin therapy during this long-term follow-up.

Methods and Results—All 214 children who initially participated in the previous placebo-controlled study were eligible for the follow-up study. After completion of the placebo-controlled study, all children continued treatment with pravastatin 20 or 40 mg, depending on their age. Blood samples were taken on a regular basis for lipids and safety parameters, and a carotid IMT measurement was performed after an average treatment period of 4.5 years. Follow-up data for 186 children were available for the statistical analyses. Multivariate analyses revealed that age at statin initiation was an independent predictor for carotid IMT after follow-up with adjustment for carotid IMT at initiation of statin treatment, sex, and duration of treatment. Early initiation of statin treatment was associated with a subsequently smaller IMT. Furthermore, no serious laboratory adverse events were reported during follow-up, and statin treatment had no untoward effects on sexual maturation.

Conclusions—These data indicate that early initiation of statin treatment delays the progression of carotid IMT in adolescents and young adults. The present study shows for the first time that early initiation of statin therapy in children with familial hypercholesterolemia might be beneficial in the prevention of atherosclerosis in adolescence. (Circulation. 2007;116:664-668.)

Key Words: adolescents ■ atherosclerosis ■ child ■ hypercholesterolemia ■ statins

Familial hypercholesterolemia (FH) is the paradigm of the established relationship between increased low-density lipoprotein cholesterol (LDL-C) and cardiovascular disease.1,2 This monogenetic disorder is characterized by exposure to severely elevated LDL-C levels from birth on,3,4 which strongly predispose to the early initiation of atherosclerosis. Indeed, children with FH are already characterized by impaired endothelial function and increased intima-media thickness (IMT).5,6 As a sequel to these observations, myocardial ischemia and coronary artery stenosis have been documented in young adults with this disorder.7,8 The early onset of atherosclerosis in patients with FH stresses the need to initiate cholesterol-lowering treatment at a young age in children with this disorder. In adults, the preferred drugs are HMG CoA reductase inhibitors or statins. In previous years, several trials have demonstrated the efficacy and short-term safety of statin therapy in children and adolescents.9–14 In one of these randomized placebo-controlled trials in children, we also have demonstrated that 2-year treatment with pravastatin reduced the progression of atherosclerosis as measured by IMT.13 Because longer-term statin studies in children are lacking, it is unknown at which age statin treatment should be initiated in terms of safety and cardiovascular disease risk reduction. Therefore, we continued to follow up the subjects of our previous study13 to explore the relationship between the age at statin initiation and carotid IMT after follow-up on statin treatment. Furthermore, we were able to evaluate the long-term effects of statin treatment on safety parameters.

Received December 7, 2006; accepted May 25, 2007.
Correspondence to Barbara A. Hutten, PhD, Academic Medical Centre, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Meibergdreef 9, Room J1B-209–1, 1105 AZ Amsterdam, The Netherlands. E-mail b.a.hutten@amc.uva.nl
© 2007 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.106.671016
Methods

Patients
All 214 patients who initially participated in the single-center, randomized, double-blind, placebo-controlled study were eligible for the present study. Briefly, children were enrolled if they had 1 parent with a definite clinical or molecular diagnosis of FH, were between 8 and 18 years of age; had been on a fat-restricted diet for at least 3 months; had fasting plasma LDL-C levels between 8 and 18 years of age; had been on a fat-restricted diet for at least 2 years after subjects had completed the placebo-controlled trial. Carotid B-mode ultrasound examinations were performed by a single sonographer with an Acuson XP128 ultrasound machine equipped with an L75 transducer (10 MHz) and extended-frequency software (Acuson-Siemens, Mountain View, Calif). Images of the distal common, bulb, and internal far-wall carotid segments were saved as JPEG stills on minidisks. The IMT was measured by a single image analyst masked to all clinical information. Mean carotid IMT was defined as the mean IMT of the right and left common carotid, carotid bulb, and internal carotid far wall segments. For a given segment, IMT was defined as the average of the right and left IMT measurements. If a segment was missing on either side, 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 the mean carotid IMT also was considered missing.

Statistical Analyses
For the statistical analyses of the present study, we used only data from the time span in which patients were on statin treatment (the Figure). For instance, carotid IMT at the initiation of statin treatment, depending on randomization and measured at baseline or at the end of the original placebo-controlled study, and currently measured IMT after follow-up were used for statistical data analyses. Using a linear regression model, we first explored the univariate association between the mean carotid IMT after follow-up and the following variables: age at statin initiation, carotid IMT at statin initiation, duration of statin treatment, statin dosage, sex, body mass index, mean arterial blood pressure, total cholesterol, LDL-C, HDL-C, and triglycerides. Using multivariate analyses, we identified independent predictors after stepwise selection in a model that constantly contained age at statin initiation. Variables with a skewed distribution were log transformed before analysis. Statistical analyses were performed with SPSS 11.5 for Windows (SPSS Inc, Chicago, Ill) software.

Results
From the original cohort of 214 children, 28 subjects were excluded from the present analysis because they moved (n=10), refused consent (n=7), or did not use statins owing to age at menarche, Tanner staging, and testicular volume, were obtained at initiation of statin treatment and at regular intervals at the outpatient clinic once or twice a year. Plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were determined by means of commercially available kits (Boehringer, Mannheim, Germany). Levels of LDL-C were calculated with the Friedewald equation. Hormone values were evaluated by means of age- and Tanner stage-specific reference values as used in the Academic Medical Centre (Amsterdam, the Netherlands).

Carotid IMT measurement. The shaded areas represent the periods in which patients were on statin treatment, and data from those periods were used for statistical analyses in the present study. R indicates randomization; RCT, randomized controlled trial.

Procedures
At the end of the previous placebo-controlled trial, children who were on pravastatin continued with pravastatin, and those who were on placebo changed to 20 or 40 mg pravastatin, depending on their age (<14 years, 20 mg; ≥14 years, 40 mg). For the present study, children were followed up for at least 2 years after they had completed the original placebo-controlled trial, which means that subjects on placebo treatment in the original study were treated with statins for at least 2 years and subjects on statin treatment for at least 4 years (the Figure). Plasma levels of lipids, muscle and liver enzymes, sex steroids, gonadotropins, and hormones of the pituitary-adrenal axis, as well as height, weight, and information with respect to age at menarche, Tanner staging, and testicular volume, were obtained at initiation of statin treatment and at regular intervals at the outpatient clinic once or twice a year. Plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were determined by means of commercially available kits (Boehringer, Mannheim, Germany). Levels of LDL-C were calculated with the Friedewald equation. Hormone values were evaluated by means of age- and Tanner stage-specific reference values as used in the Academic Medical Centre (Amsterdam, the Netherlands).

Carotid IMT was measured at the initiation of statin treatment and at least 2 years after subjects had completed the placebo-controlled trial. Carotid B-mode ultrasound examinations were performed by a single sonographer with an Acuson XP128 ultrasound machine equipped with an L75 transducer (10 MHz) and extended-frequency software (Acuson-Siemens, Mountain View, Calif). Images of the distal common, bulb, and internal far-wall carotid segments were saved as JPEG stills on minidisks. The IMT was measured by a single image analyst masked to all clinical information. Mean carotid IMT was defined as the mean IMT of the right and left common carotid, carotid bulb, and internal carotid far wall segments. For a given segment, IMT was defined as the average of the right and left IMT measurements. If a segment was missing on either side, 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 the mean carotid IMT also was considered missing.

Statistical Analyses
For the statistical analyses of the present study, we used only data from the time span in which patients were on statin treatment (the Figure). For instance, carotid IMT at the initiation of statin treatment, depending on randomization and measured at baseline or at the end of the original placebo-controlled study, and currently measured IMT after follow-up were used for statistical data analyses. Using a linear regression model, we first explored the univariate association between the mean carotid IMT after follow-up and the following variables: age at statin initiation, carotid IMT at statin initiation, duration of statin treatment, statin dosage, sex, body mass index, mean arterial blood pressure, total cholesterol, LDL-C, HDL-C, and triglycerides. Using multivariate analyses, we identified independent predictors after stepwise selection in a model that constantly contained age at statin initiation. Variables with a skewed distribution were log transformed before analysis. Statistical analyses were performed with SPSS 11.5 for Windows (SPSS Inc, Chicago, Ill) software.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
From the original cohort of 214 children, 28 subjects were excluded from the present analysis because they moved (n=10), refused consent (n=7), or did not use statins owing...
to pregnancy (n=6) or otherwise unknown reasons (n=4), and 1 male adolescent had died after a motorcycle accident. Mean age at statin initiation of the remaining 186 subjects was 13.7±3.1 years, and 49% were male. The lipid profiles at initiation of statin treatment and after follow-up are depicted in Table 1. Mean carotid IMT was 0.494±0.047 mm at the start of statin treatment and 0.547±0.060 mm after follow-up. Mean duration of statin treatment was 4.5 years (range, 2.1 to 7.4 years). During follow-up, 83% of the patients continued with pravastatin, and 17% changed to another type of statin. None of the subjects had cardiovascular complaints or a cardiovascular event during follow-up.

The results of the univariate and multivariate analyses of the association between carotid IMT after follow-up and clinical variables are shown in Table 2. The following independent predictors for combined carotid IMT after follow-up were identified: carotid IMT at statin initiation (β=0.446±0.088; P<0.001), age at statin initiation (β=0.003±0.001; P=0.016), male sex (β=0.027±0.008; P<0.001), and duration of statin use (β=0.013±0.003; P<0.001). Although mean arterial blood pressure and HDL-C levels at the start of statin use were significantly associated in the univariate analyses, these relationships were lost in the multivariate analyses.

### Safety

No serious laboratory adverse events were reported during the follow-up period, and none of the subjects discontinued treatment as a result of laboratory adverse events. Two male subjects, both extreme fitness practitioners, showed increased creatinine phosphokinase levels of >10 times the upper limit of normal. Creatinine phosphokinase levels returned to normal without the discontinuation of treatment, and the extreme physical exercise was consequently judged to be the cause for these increases. Four other subjects complained of myalgia, but this was not accompanied by elevated creatinine phosphokinase levels.

One boy who was 12 years of age was still prepubertal, and 4 girls who were 12.5, 13.8, 14.0, and 14.2 years of age had not experienced their menarche at the end of this follow-up period. Three male subjects and 1 female participant showed increased levels of follicle stimulation hormone just above the normal range. However, because follicle stimulation hormone does not directly regulate steroid synthesis, these elevations are not likely to be related to statin use. Three subjects showed levels of dehydroepiandrosterone sulfate below the normal range, which was considered not clinically relevant as evidenced by normal pubertal development and normal adrenocorticotropic hormone and cortisol levels. Two subjects had slightly higher-than-normal adrenocorticotropic

### Table 2

| Lipid Profile at the Start of Statin Treatment and After Follow-Up in 186 FH Children |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Start Statin, mmol/L | End of Follow-Up, mmol/L | Change From Start Statin, % |
| Total cholesterol               | 7.76±1.48         | 5.95±1.29         | −22.5±15.2       |
| LDL-C                           | 6.09±1.44         | 4.26±1.21         | −29.2±17.3       |
| HDL-C                           | 1.27±0.27         | 1.29±0.31         | 3.1±21.8         |
| Triglycerides                   | 0.76 (0.51, 1.13) | 0.75 (0.56, 1.05) | −1.9 (−27.2, 43.6) |

Values are expressed as mean±SD except for triglycerides, which are expressed as median (interquartile range).

### Table 2: Association Between Various Determinants Measured at Statin Initiation and the Combined Carotid IMT After Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression Coefficient (SE)</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>0.003 (0.001)</td>
<td>0.029</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.033 (0.009)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.002 (0.001)</td>
<td>0.132</td>
</tr>
<tr>
<td>Mean arterial blood pressure*</td>
<td>0.001 (0.001)</td>
<td>0.10</td>
</tr>
<tr>
<td>Combined IMT</td>
<td>0.544 (0.088)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.005 (0.003)</td>
<td>0.143</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.007 (0.004)</td>
<td>0.069</td>
</tr>
<tr>
<td>HDL-C</td>
<td>−0.038 (0.014)</td>
<td>0.008</td>
</tr>
<tr>
<td>Triglycerides†</td>
<td>0.016 (0.009)</td>
<td>0.094</td>
</tr>
<tr>
<td>Statin dosage 40 vs 20 mg</td>
<td>−0.019 (0.016)</td>
<td>0.252</td>
</tr>
<tr>
<td>Duration of statin treatment</td>
<td>0.010 (0.004)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Mean arterial blood pressure = (systolic blood pressure + 2×diastolic blood pressure)/3.
†Triglycerides were log transformed before statistical analysis.
hormone levels, but these levels were possibly due to stressful venipunctures.

Discussion
In this longest follow-up study of statin therapy in childhood to date, we demonstrate that, after adjustment for potential confounders, age at statin initiation was positively associated with carotid IMT after follow-up on statin treatment. This finding indicates that the earlier statin treatment is initiated, the smaller the carotid IMT is later. According to our model, IMT after follow-up will increase 0.003 mm in FH patients for each year that statin therapy is postponed (Table 2). Furthermore, we carefully checked adverse events and untoward influences on pubertal development and hormonal status. Given that all calculated median plasma hormone concentrations (steroid hormones, gonadotropins, and adrenocorticotropic hormone) were in a range similar to the reference medians and that the few unexplained outliers probably reflect normal statistical variation, we consider it unlikely that statin treatment in these young subjects affects hormonal regulation and sexual maturation.

The primary goal of the active identification programs in both the Netherlands and the United Kingdom is to ensure that lipid-lowering treatment is initiated as early as possible. Our data support the concept that this initiation should occur in childhood. This concept is further supported by the favorable safety outcomes, which indicate that this therapy had no untoward effects on sexual maturation or growth. In addition, side effects such as myopathy were rare. On the other hand, the optimal age at which statin treatment could be started during childhood is unknown, and long-term follow-up of patients who receive early treatment is needed to confirm the benefit of early treatment and to identify the optimal age at which treatment should be started.

Some methodological aspects of our study merit discussion. After finishing the original 2-year trial, all children received open-label pravastatin treatment. Because treatment during the follow-up period was not placebo controlled, safety outcomes were not evaluated in the preferred controlled setting, which may have affected our findings with respect to safety and pubertal development. However, variations in hormone levels, growth, and sexual maturation were individually judged and compared with reference values according to age, sex, and pubertal stage.

The active identification of FH patients is gaining acceptance across Europe. This will undoubtedly lead to increasing numbers of FH children coming under medical attention. Our results are likely to be useful in the counseling of these young children and their parents and in the motivation for compliance with drug therapy. Longer-term follow-up treatment with more robust lipid-lowering therapy is now required to assess whether arterial wall morphology in FH individuals can be restored to non-FH pediatric or young adult ranges with the inference that cardiovascular risk in this high-risk cardiovascular disease population can be similarly ameliorated.

Acknowledgments
We thank H.R. Büller for reading the manuscript carefully and J. Gort for excellently performing all ultrasound measurements.

Source of Funding
This study has been funded by Bristol-Myers Squibb. The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Disclosures
Dr. Kastelein has received consulting fees, lecture fees, and grant support from Pfizer, Merck, Schering-Plough, AstraZeneca, Bristol-Myers Squibb, and Sankyo. The other authors report no conflicts.

References
13. Wiegman A, Huttner BA, de Groot E, Rodenburg J, Bakker HD, Builer HR, Stijbrants EJ, Kastelein JJ. Efficacy and safety of statin therapy in


**CLINICAL PERSPECTIVE**

Familial hypercholesterolemia (FH) is the most common monogenetic disorder, affecting $\approx$1 in 500 individuals in its heterozygous form. It leads to severely elevated plasma low-density lipoprotein cholesterol from birth on, causing premature atherosclerosis and cardiovascular disease. Evidence-based guidelines from the National Cholesterol Education Program are available for the treatment of adult FH patients. Except for some recommendations, such guidelines are not available for children because studies with an appropriate follow-up are lacking. Consequently, physicians have been uncertain whether, when, and how to treat children with FH. Here, we report the data of 186 children 8 to 18 years of age who were treated with statin for an average of 4.5 years. This longest follow-up study to date demonstrates that age at statin initiation is positively associated with carotid status after follow-up. These data strongly indicate that early statin treatment reduces atherosclerotic burden more vigorously than treatment started later, supporting the concept that statin treatment should be initiated in childhood. This finding is further strengthened by favorable safety with no untoward effects on sexual maturation or growth. In conclusion, our data support early initiation of statin therapy in FH children, which might be beneficial in the prevention of atherosclerosis in later life. Although the optimal age at which statin treatment should be started during childhood is unknown, in our opinion statin treatment should be considered for all children who are $>$8 years of age once FH has been diagnosed.
Statin Treatment in Children With Familial Hypercholesterolemia: The Younger, the Better
Jessica Rodenburg, Maud N. Vissers, Albert Wiegman, A. S. Paul van Trotsenburg, Anouk van der Graaf, Eric de Groot, Frits A. Wijburg, John J.P. Kastelein and Barbara A. Hutten

Circulation. 2007;116:664-668; originally published online July 30, 2007;
doi: 10.1161/CIRCULATIONAHA.106.671016

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 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/116/6/664

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/