ORIGINAL ARTICLE

20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia

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ABSTRACT

BACKGROUND

Familial hypercholesterolemia is characterized by severely elevated low-density lipoprotein (LDL) cholesterol levels and premature cardiovascular disease. The short-term efficacy of statin therapy in children is well established, but longer follow-up studies evaluating changes in the risk of cardiovascular disease are scarce.

METHODS

We report a 20-year follow-up study of statin therapy in children. A total of 214 patients with familial hypercholesterolemia (genetically confirmed in 98% of the patients), who were previously participants in a placebo-controlled trial evaluating the 2-year efficacy and safety of pravastatin, were invited for follow-up, together with their 95 unaffected siblings. Participants completed a questionnaire, provided blood samples, and underwent measurements of carotid intima–media thickness. The incidence of cardiovascular disease among the patients with familial hypercholesterolemia was compared with that among their 156 affected parents.

RESULTS

Of the original cohort, 184 of 214 patients with familial hypercholesterolemia (86%) and 77 of 95 siblings (81%) were seen in follow-up; among the 214 patients, data on cardiovascular events and on death from cardiovascular causes were available for 203 (95%) and 214 (100%), respectively. The mean LDL cholesterol level in the patients had decreased from 237.3 to 160.7 mg per deciliter (from 6.13 to 4.16 mmol per liter) — a decrease of 32% from the baseline level; treatment goals (LDL cholesterol <100 mg per deciliter [2.59 mmol per liter]) were achieved in 37 patients (20%). Mean progression of carotid intima–media thickness over the entire follow-up period was 0.0056 mm per year in patients with familial hypercholesterolemia and 0.0057 mm per year in siblings (mean difference adjusted for sex, −0.0001 mm per year; 95% confidence interval, −0.0010 to 0.0008). The cumulative incidence of cardiovascular events and of death from cardiovascular causes at 39 years of age was lower among the patients with familial hypercholesterolemia than among their affected parents (1% vs. 26% and 0% vs. 7%, respectively).

CONCLUSIONS

In this study, initiation of statin therapy during childhood in patients with familial hypercholesterolemia slowed the progression of carotid intima–media thickness and reduced the risk of cardiovascular disease in adulthood. (Funded by the AMC Foundation.)

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N Engl J Med 2019;381:1547-56.
DOI: 10.1056/NEJMoa1816454

Familial hypercholesterolemia is a common autosomal dominant disorder of lipoprotein metabolism. It is caused by mutations in genes encoding key proteins involved in the low-density lipoprotein (LDL) receptor endocytic and recycling pathways that lead to decreased cellular uptake of LDL cholesterol. Consequently, severely elevated plasma levels of LDL cholesterol develop from birth onward in patients with familial hypercholesterolemia, and these patients are at high risk for premature cardiovascular disease.[1]

Statins are the preferred pharmacologic therapy for familial hypercholesterolemia. Because the first functional and morphologic changes of the arterial wall occur in childhood,[2,3] there is universal agreement that treatment should start at a young age. The European Atherosclerosis Society (EAS) consensus panel and the current American College of Cardiology–American Heart Association guidelines for familial hypercholesterolemia advocate initiation of statins from as young as 8 years[4] or 10 years[5] of age, respectively.

Although the lipid-lowering effect of statin therapy is well established in children,[6] proper follow-up data on outcomes in treated children into adulthood to evaluate the risk of cardiovascular disease are lacking. In adults with familial hypercholesterolemia, the benefit of statin treatment in the prevention of cardiovascular disease has only been shown retrospectively.[7,8] Furthermore, most patients who were treated were not genetically tested, and some might not actually have familial hypercholesterolemia. Therefore, although familial hypercholesterolemia is a prevalent disorder characterized by an extremely high risk of cardiovascular disease, important gaps in the evidence favoring treatment appear to be present.

In the present study, we aimed to address differential progression in both subclinical atherosclerosis and clinical cardiovascular disease in patients with familial hypercholesterolemia who started statin treatment in childhood, and to compare the outcomes with those in both patients with untreated familial hypercholesterolemia and healthy persons. We therefore performed a 20-year follow-up study involving children with genetically defined familial hypercholesterolemia who started statin therapy at an age of 8 to 18 years. Follow-up occurred well into adulthood, at an age when their affected parents may have already had a cardiovascular event. We assessed subclinical atherosclerosis progression over time by comparing the carotid intima–media thickness in patients with familial hypercholesterolemia with that in their unaffected age-matched siblings. The incidence of cardiovascular disease among the (now adult) patients with familial hypercholesterolemia was compared with that among their parents with familial hypercholesterolemia for whom statins were only available much later in life.

Methods

Study Oversight

The study protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at the University of Amsterdam, and all the participants provided written informed consent. The authors designed the study, gathered and analyzed the data, and wrote the manuscript. All the authors revised the manuscript, vouch for the accuracy and completeness of the data, and made the decision to submit the manuscript for publication. There was no commercial support for this study.

Study Population and Design

All 214 children with familial hypercholesterolemia who had undergone randomization from 1997 through 1999 in a single-center, double-blind, placebo-controlled trial, which evaluated the 2-year efficacy and safety of pravastatin, were eligible for the current study. The trial design has been published previously.[9] All the children were genetically tested; 210 (98%) had a documented pathogenic mutation in the genes encoding LDL receptor or apolipoprotein B. After the intervention phase, pravastatin was given to both treatment groups. Children were subsequently seen at the pediatric lipid clinic of the academic medical center until they were transitioned to an adult lipid clinic or general practitioner. Although not described in the original report of the trial results, 95 unaffected siblings were enrolled at baseline as a control group. These siblings had all been genetically tested, and familial hypercholesterolemia was excluded. These siblings were also eligible for the current study. In addition, information on cardiovascu-

lar events and death from cardiovascular causes in the affected parents was collected. Participating children were members of 156 unique families; each child had a parent with confirmed familial hypercholesterolemia.

We contacted all eligible patients and their unaffected siblings approximately 20 years after the trial was initiated. Those who agreed to participate were invited for a single hospital visit. Before that visit, a questionnaire was sent to document medical history, lifestyle habits, medication use, and family history. During the visit, participants underwent a physical examination, a fasting blood sample was obtained, and the carotid intima–media thickness was measured. A short telephone interview about outcome measures was used for those participants who were unable to visit the hospital or who did not return the questionnaire.

LIPIDS AND LIPOPROTEINS

Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined with commercially available kits (Cobas c502 and c702 chemical analyzers, Roche Diagnostics), and the LDL cholesterol level was calculated with the Friedewald equation.[10] Plasma concentrations of apolipoprotein B-100 and apolipoprotein A-I were measured by standard methods. Patients with familial hypercholesterolemia were considered to be "on target" if their LDL cholesterol levels were less than 70 mg per deciliter (1.81 mmol per liter) (in those with cardiovascular disease) or less than 100 mg per deciliter (2.59 mmol per liter) (in those without cardiovascular disease).

CAROTID INTIMA–MEDIA THICKNESS

Carotid ultrasonographic measurements of intima–media thickness were performed according to standardized and validated procedures, as described previously.[3,9,11] A single experienced sonographer assessed all carotid ultrasonographic scans over time; thus, a given patient had the same sonographer throughout the study. Initial carotid ultrasonographic examinations were performed with an Acuson 128XP/10 and an L7 EF (5 to 7 MHz, linear array extended frequency) vascular transducer (Siemens). In the follow-up ultrasonographic measurements, an Acuson Aspen instrument equipped with (the same) L7 transducer was used. The standardization of equipment with the use of phantom and repeat human scans is described in the Methods section in the Supplementary Appendix (available at NEJM.org). Three certified image analysts analyzed the scans. Analysts were assigned to a given participant throughout the study. Sonographers and analysts were unaware of the demographic and clinical characteristics of the participants. Mean carotid intima–media thickness was defined as the average of the mean values for intima–media thickness in the right and left common carotid, the carotid bulb, and the internal carotid far-wall segments.

CARDIOVASCULAR EVENTS AND DEATH FROM CARDIOVASCULAR CAUSES

Prespecified outcomes were cardiovascular disease and death from cardiovascular causes. Cardiovascular disease was defined as the presence of a myocardial infarction, angina pectoris, peripheral artery disease, or stroke (all diagnosed by medical professionals) or a coronary revascularization procedure (percutaneous transluminal coronary angioplasty or coronary-artery bypass grafting). All outcomes were centrally adjudicated. If there was any doubt about the medical history regarding cardiovascular outcomes of those patients who were not treated in our hospital, we obtained their permission in all cases to collect relevant information from their treating physician or hospital. We had access to the relevant medical history of the affected parents in all cases through the referral letters of their family physician or the specialist treating them.

STATISTICAL ANALYSIS

Differences and 95% confidence intervals in demographic and clinical characteristics between patients with familial hypercholesterolemia and their unaffected siblings were evaluated with the use of generalized estimating equations to account for correlations within families (exchangeable correlation structure). A linear mixed-effects model with a random-effects term for family and image analyst was used to evaluate the difference in carotid intima–media thickness between patients with familial hypercholesterolemia and their unaffected siblings. Potential confounders were included in the linear mixed-effects model (full model). With the use of stepwise

backward elimination, a final model, which always contained the variable of status with respect to familial hypercholesterolemia (yes or no), was derived (see the Methods section in the Supplementary Appendix).

A linear mixed-effects model with a random-effects term for family and participant was used to assess the difference in the rate of change in carotid intima–media thickness between the groups. To estimate this change more accurately, we also included measurements of carotid intima–media thickness that were made 10 years after the start of the trial, if available (see the Methods section in the Supplementary Appendix).[12]

Cumulative Kaplan–Meier survival curves were constructed to explore the differences in time to first cardiovascular event or time to death from cardiovascular causes between children with familial hypercholesterolemia and their affected parents. For the outcome of time to first cardiovascular event, follow-up started at birth and ended for each participant at the date of the first cardiovascular event or the date of the visit or telephone interview, whichever came first. Similarly, time to death from cardiovascular causes was defined as the period from the year of birth to the year of death, or data were censored at the date when the questionnaire was returned or the telephone interview was conducted. Cox regression analyses were performed to calculate hazard ratios with 95% confidence intervals and to adjust for potential confounders (i.e., sex and smoking). A random-effects term (frailty) was added to the model to account for correlations within the family (see the Methods section in the Supplementary Appendix).

In our study protocol, we did not specify a method for controlling type I error with multiple comparisons. Therefore, most estimates of association include point estimates with 95% confidence intervals.

All statistical tests were two-sided. Statistical analyses were performed with SPSS software, version 24.0 (SPSS); the SAS statistical package release, version 9.2 (SAS Institute); and R statistics, version 3.0.1 (R Foundation for Statistical Computing).

RESULTS

DESCRIPTION OF THE STUDY GROUPS

Of the original cohort of 214 children with familial hypercholesterolemia, 1 died during the

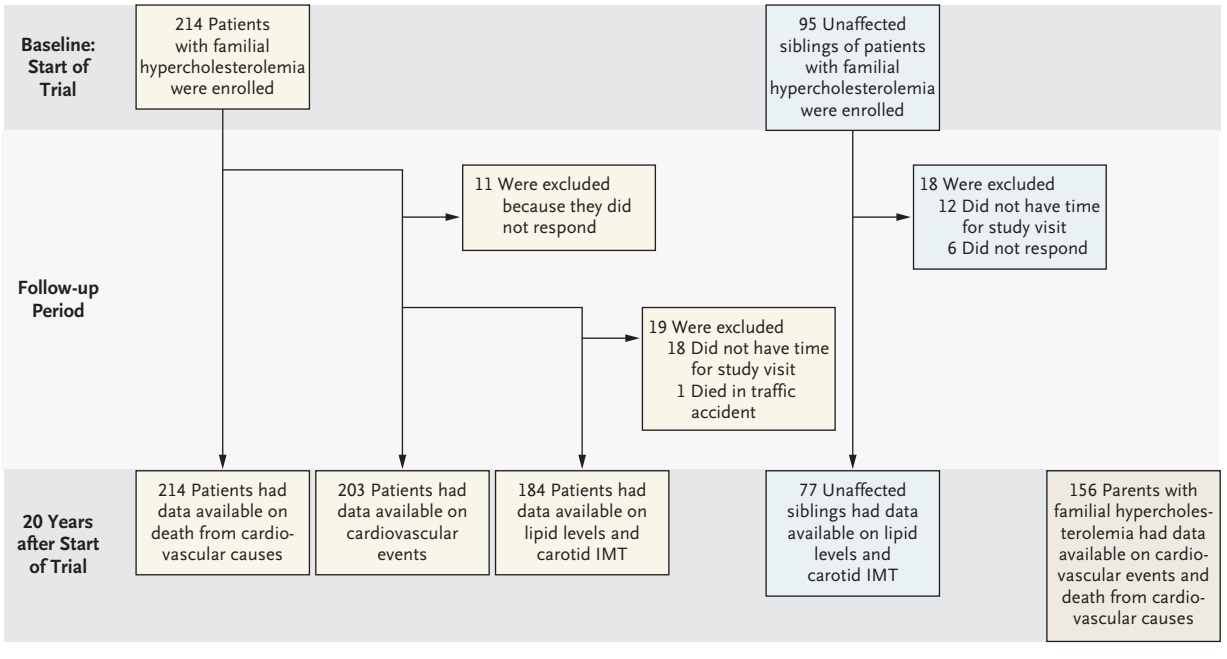

Figure 1. Study Flow.
IMT denotes intima–media thickness.

trial after a traffic accident at 15 years of age, leaving 213. At 20 years after initiation of the original trial, 184 patients with familial hypercholesterolemia (86% of the original cohort) were seen in the hospital and 18 (8%) responded to the questionnaire by telephone; the remaining 11 patients (5%) did not respond. For these 11 patients, information on vital status was available. Of the 95 siblings, 77 (81%) visited the hospital and 12 (13%) responded to the questionnaire; the remaining 6 (6%) did not respond (Fig. 1).

Demographic and clinical characteristics at baseline for the original cohort and follow-up cohort are shown in Table 1, and in Tables S1 and S2 in the Supplementary Appendix. The mean duration of follow-up was 18 years (range, 15 to 21), and the mean (±SD) age at follow-up was 31.7±3.2 years for the patients with familial hypercholesterolemia and 31.6±3.0 years for the siblings (mean difference, 0.1 year; 95% confidence interval [CI], −0.9 to 0.6). At follow-up, 41 patients with familial hypercholesterolemia (22%) and 26 siblings (34%) were smokers

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline and at 20-Year Follow-up.*

Characteristic	At Baseline			At Follow-up		
	Patients with FH (N=214)	Unaffected Siblings (N=95)	Difference (95% CI)†	Patients with FH (N=184)	Unaffected Siblings (N=77)	Difference (95% CI)†
Age — yr	13.0±2.9	12.9±2.9	0.1 (−0.8 to 0.6)	31.7±3.2	31.6±3.0	0.1 (−0.9 to 0.6)
Male sex — no. (%)	100 (47)	50 (53)	−6 (−18 to 6)	88 (48)	43 (56)	−8 (−21 to 5)
Height — m	1.57±0.15	1.57±0.15	0.00 (−0.05 to 0.03)	1.75±0.10	1.76±0.09	−0.01 (−0.04 to 0.01)
Weight — kg	49.4±15.1	48.7±16.6	0.7 (−3.3 to 4.6)	77.6±14.6	79.4±14.2	−1.7 (−5.5 to 2.1)
Body-mass index‡	19.6±3.6	19.1±3.7	0.5 (−0.4 to 1.4)	25.3±4.2	25.5±3.9	−0.2 (−1.2 to 0.9)
Blood pressure — mm Hg						
Systolic	110.2±12.4	110.1±12.0	0.1 (−2.8 to 3.0)	121.0±12.3	121.5±12.5	−0.5 (−3.8 to 2.8)
Diastolic	61.5±8.6	62.2±8.5	−0.8 (−2.8 to 1.3)	74.2±8.1	75.1±9.0	−0.9 (−3.2 to 1.4)
Risk factors — no. (%)						
Diabetes	0	0	—	1 (1)	2 (3)	−2 (−6 to 2)
Hypertension	0	0	—	16 (9)	10 (13)	−4 (−13 to 4)
Current smoking	24 (11)	6 (6)	5 (−2 to 11)	41 (22)	26 (34)	−11 (−24 to 1)
Statin use — no. (%)	0	0	—	146 (79)	1 (1)	78 (70 to 83)
Cholesterol — mg/dl						
Total	300.6±51.3	166.9±24.9	133.7 (125.1 to 147.0)	232.6±75.6	201.5±38.6	31.1 (125.1 to 147.0)
LDL	237.3±50.0	98.5±22.1	138.8 (130.7 to 147.0)	160.7±72.6	121.9±37.0	38.8 (25.5 to 52.1)
HDL	47.8±10.7	54.8±13.8	−7.0 (−10.2 to −3.7)	53.3±13.9	56.3±16.1	−3.0 (−7.1 to 1.1)
Apolipoprotein — mg/dl						
B-100	141.2±30.7	82.7±18.4	58.5 (52.8 to 64.2)	117.7±41.5	95.1±28.6	22.6 (13.9 to 31.4)
A-I	124.7±19.3	137.8±24.6	−13.1 (−19.1 to −7.1)	151.7±38.5	161.5±38.5	−9.9 (−20.1 to 0.4)
Lipoprotein(a) — mg/liter§						
Median	121	79	20 (−43 to 83)	141	96	31 (−47 to 108)
Interquartile range	46 to 265	37 to 248		64 to 299	48 to 326	

* Plus–minus values are means ±SD. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. CI denotes confidence interval, FH familial hypercholesterolemia, HDL high-density lipoprotein, and LDL low-density lipoprotein.
† For continuous variables, the difference in means is shown. For dichotomous variables, the absolute difference in percentage points is shown.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Additional information on lipoprotein(a) measurements is available in the Supplementary Appendix (Methods section and Table S1).

(difference, –11 percentage points; 95% CI, –24 to 1).

Of the patients with familial hypercholesterolemia, 146 (79%) stated that they were using lipid-lowering medication and 123 (84%) of those reported that they had taken 80% or more of their prescribed medication in the month before our reassessment. (Details on the type and dose of medication are provided in Table S3 in the Supplementary Appendix.) Statin therapy in this group was initiated at a mean age of 14.0±3.1 years. Patients who had stopped taking statins did not differ significantly from those who had continued taking them with respect to sex, age, body-mass index, or smoking habits. Four patients had discontinued statin therapy because of side effects. No episodes of noted rhabdomyolysis or other serious adverse events were reported. There were no significant differences in the results of liver-function tests (levels of aspartate aminotransferase and alanine aminotransferase) or creatine kinase levels between patients with familial hypercholesterolemia and their unaffected siblings.

The original cohort of children with familial hypercholesterolemia came from 156 different families. Because statins were introduced in 1988, the 156 parents affected by familial hypercholesterolemia (59% male) could not have started statin therapy earlier than a mean age of 32±3 years (range, 20 to 51).

LIPIDS AND LIPOPROTEINS

Plasma levels of lipids and lipoproteins in the patients with familial hypercholesterolemia and their unaffected siblings at baseline and at follow-up are shown in Table 1 and Figure 2, and in Tables S1 and S2 in the Supplementary Appendix. The mean LDL cholesterol level at follow-up was 160.7±72.6 mg per deciliter (4.16±1.88 mmol per liter) in patients with familial hypercholesterolemia and 121.9±37.0 mg per deciliter (3.15±0.96 mmol per liter) in siblings (mean difference, 38.8 mg per deciliter; 95% CI, 25.5 to 52.1 [1.00 mmol per liter; 95% CI, 0.66 to 1.35]). These levels represented a decrease of 32% and an increase of 24% from the baseline levels in patients with familial hypercholesterolemia and their unaffected siblings, respectively.

At follow-up, 37 patients with familial hypercholesterolemia (20%) reached the LDL cholesterol treatment target of less than 100 mg per deciliter. Eight of those 37 reached LDL cholesterol levels of less than 70 mg per deciliter.

CAROTID INTIMA–MEDIA THICKNESS

At baseline in the original trial, patients with familial hypercholesterolemia had a greater carotid intima–media thickness than their unaffected siblings (mean, 0.446 mm [95% CI, 0.439 to 0.453] vs. 0.439 mm [95% CI, 0.430 to 0.449]; mean difference adjusted for age and sex, 0.012 mm [95% CI, 0.002 to 0.021]) (Table S4 in the Supplementary Appendix). After 20 years, the mean thickness was 0.555 mm (95% CI, 0.542 to 0.567) in the patients with familial hypercholesterolemia and 0.551 mm (95% CI, 0.531 to 0.570) in their unaffected siblings (mean difference adjusted for age, sex, mean arterial blood pressure, and baseline carotid intima–media thickness, 0.008 mm; 95% CI, –0.009 to 0.026). The patients with familial hypercholesterolemia who were considered to have reached the LDL cholesterol treatment target had a mean carotid intima–media thickness of 0.532 mm (95% CI, 0.508 to 0.556); among patients with familial hypercholesterolemia who were not considered to have reached the LDL cholesterol treatment target, the value was 0.560 mm (95% CI, 0.546 to 0.574)

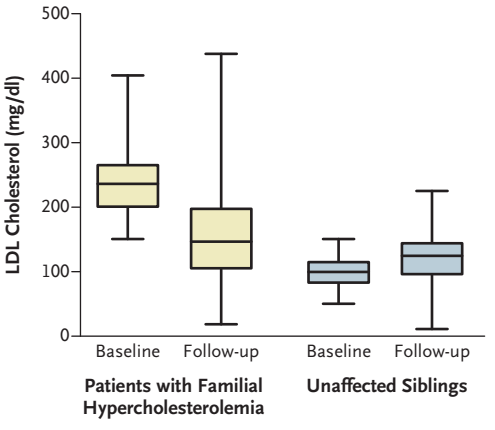

Figure 2. Low-Density Lipoprotein (LDL) Cholesterol Levels of Patients with Familial Hypercholesterolemia and Their Unaffected Siblings at Baseline and at Follow-up.

The top and bottom borders of each box indicate the interquartile range, the horizontal bar within each box indicates the median, and the I bars indicate the range of observations. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

(mean difference adjusted for mean arterial blood pressure and baseline carotid intima–media thickness, 0.022 mm; 95% CI, 0.003 to 0.047). During follow-up, the rate of progression in mean carotid intima–media thickness was 0.0056 mm (95% CI, 0.0051 to 0.0061) per year in the patients with familial hypercholesterolemia and 0.0057 mm (95% CI, 0.0050 to 0.0065) per year in their unaffected siblings (mean difference adjusted for sex, −0.0001 mm per year; 95% CI, −0.0010 to 0.0008).

CARDIOVASCULAR EVENTS

Information on cardiovascular events was obtained for 203 patients with familial hypercholesterolemia (95%); 1 had had angina pectoris and underwent percutaneous coronary intervention at 28.6 years of age. He was a nonsmoker who had stopped taking the trial drug at the end of the trial.

In the group of 156 parents with familial hypercholesterolemia, 41 (26%) had had a cardiovascular event before 40 years of age. The majority had a myocardial infarction (27 parents; 66%) or angina pectoris (7 parents; 17%). The youngest affected parent had a myocardial infarction at 20 years of age. There was no significant difference in smoking habits between the parents who had an event and those who did not. Although we do not have information about the LDL cholesterol levels of the parents, the children of the parents who had an event had a slightly higher mean LDL cholesterol level at baseline (253±58 mg per deciliter [6.54±1.50 mmol per liter], as compared with 232±46 mg per deciliter [6.00±1.19 mmol per liter] in the children of the parents who did not have an event; mean difference, 21 mg per deciliter; 95% CI, 4 to 37 [0.54 mmol per liter; 95% CI, 0.10 to 0.96]). The cumulative cardiovascular disease–free survival at 39 years of age was 99% among patients with familial hypercholesterolemia who had begun receiving statin therapy during childhood and 74% among their affected parents (hazard ratio with adjustment for sex and smoking status, 11.8; 95% CI, 3.0 to 107.0) (Fig. 3A).

DEATH FROM CARDIOVASCULAR CAUSES

Information on death from cardiovascular causes was obtained for 100% of the patients with familial hypercholesterolemia; none of the young adults who had received treatment since child-

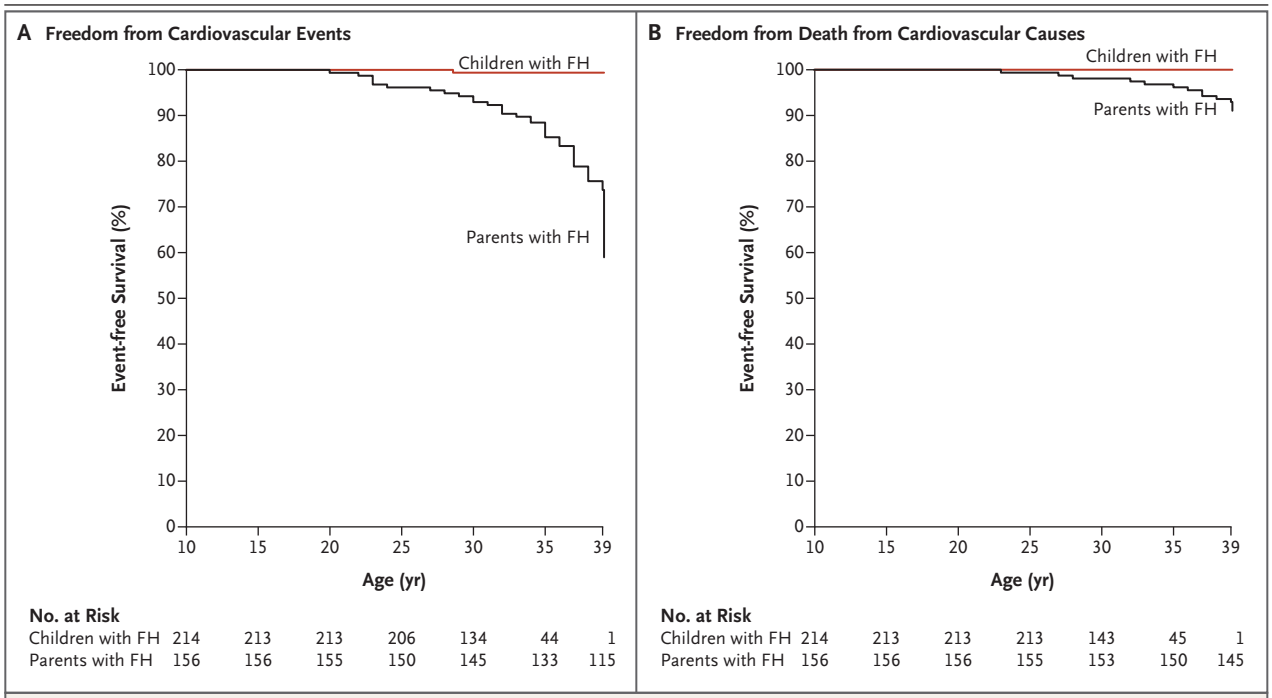

Figure 3. Kaplan–Meier Curves for Patients with Familial Hypercholesterolemia (FH) Who Began Receiving Statin Therapy during Childhood and Their Affected Parents for Whom Statins Were Available Much Later in Life.

hood died from cardiovascular disease during follow-up. In the group of affected parents, 11 of 156 (7%) died before 40 years of age, all from myocardial infarction. One parent died at 23 years of age. In the whole cohort, the cumulative percentage of persons who were free from death from cardiovascular causes at 39 years of age was 100% among patients with familial hypercholesterolemia who had received treatment since childhood and 93% among their affected parents (Fig. 3B).

DISCUSSION

In the present study, we found that 20 years after enrollment in a pediatric placebo-controlled statin trial, participants with genetically defined familial hypercholesterolemia had a mean progression of carotid intima–media thickness similar to that of their unaffected siblings. The mean LDL cholesterol level in the patients with familial hypercholesterolemia had decreased by 32% since baseline in the original trial. Furthermore, the cumulative incidence of cardiovascular events and of death from cardiovascular causes was lower among the participants with familial hypercholesterolemia than among their affected parents for whom statins were available much later in life.

These results extend previously available observational data on patients with familial hypercholesterolemia who began receiving statin therapy during childhood and constitute follow-up in real-life clinical practice. In a Norwegian cohort study, 67 patients with familial hypercholesterolemia (mean age, 25 years) were followed for a decade after participation in a trial of lipid-lowering medication.[13] In a French study, medical files of 185 children with familial hypercholesterolemia were investigated 2 years after they had begun receiving pravastatin.[14] LDL cholesterol levels in our study were similar to those in the Norwegian study, but they were lower, despite our far longer follow-up, than in the French study. In the Norwegian study, 28% of the patients were lost to follow-up, and treatment goals were achieved in only 9% of the patients. In contrast, LDL cholesterol treatment targets were achieved in 20% of the patients with familial hypercholesterolemia in our cohort, which is on par with the findings in a large cross-sectional study in the Netherlands, in which treatment goals were reached in 21% of the patients with familial hypercholesterolemia.[15]

We speculate that the failure to achieve LDL cholesterol target levels in these other two studies might be explained by the hesitation of physicians, patients, or both to use the most potent therapy available, as previously underlined in a study by Pijlman et al.[15] Another reason for not reaching target levels might be explained by the facts that baseline LDL cholesterol levels in some patients were very high and that more potent lipid-lowering therapies, such as inhibitors of proprotein convertase subtilisin–kexin type 9, were either not yet available or not commonly prescribed. The high percentage of patients in the present study in whom treatment targets were not achieved is also remarkable, since a reasonable percentage of our patients claimed to be adherent to their lipid-lowering medication. However, it could be argued that adherence to lipid-lowering medication was reported by the patients and was therefore overestimated.

The most recent consensus from the EAS and the International Society of Atherosclerosis (ISA) stated that, on the basis of the available evidence, the LDL hypothesis is no longer a hypothesis and can be considered a fact.[16,17] In addition, mendelian randomization studies show that the consequences of LDL cholesterol with respect to the development of atherosclerotic vascular disease are determined not only by the absolute LDL cholesterol level but also by the cumulative exposure of the arterial wall to LDL cholesterol.[18] Altogether, this makes a strong case for not only "the lower the better" but also for "the younger the better." The present study, involving a genetically defined cohort, is therefore of importance because it serves as a validation of the results of the mendelian randomization studies involving patients with familial hypercholesterolemia in regular clinical practice who started treatment in childhood.

Despite the modest percentage of patients with familial hypercholesterolemia in whom treatment goals were achieved, our findings suggest a positive effect on both the studied surrogate marker (carotid intima–media thickness) and on hard cardiovascular disease outcomes. Adherence at the end of the original trial[9] and after 5 years[19] and 10 years[12] of follow-up was even better than reported in the present study, so we presume that the majority of patients were taking statins

for most of the follow-up period. Thus, we deduced that starting statin treatment in childhood had beneficial effects on atherosclerotic vascular disease in participants in the present study, even when guideline goals were not always achieved. If corroborated, such findings would underscore the current pediatric guidelines, which recommend starting treatment from the age of 8 years[4] or 10 years,[5] with less stringent targets than those for adults.

The present study has certain limitations, the most important of which is its observational nature. Nevertheless, our study included long-term follow-up of children who received statins and also included a control group of unaffected siblings and a comparison with affected parents. By the inclusion of siblings as a comparison group, environmental and genetic differences between patients with familial hypercholesterolemia and controls may be diminished; consequently, the core difference between these groups reflected the presence of familial hypercholesterolemia and statin treatment. Our findings suggest that statin therapy in these patients with familial hypercholesterolemia reduced the progression of carotid intima–media thickness to a level similar to that of their siblings; this appears to constitute an important step toward future cardiovascular risk reduction, since carotid intima–media thickness is a well-validated surrogate marker for future cardiovascular risk.[20] A placebo-controlled, randomized, controlled trial of 20 years' duration in this population would have been ideal but unethical. Studying affected parents as an additional control group for the outcomes of cardiovascular events and death from cardiovascular causes is an appropriate substitute, since the parents were, in principle, a placebo group until adulthood, albeit not concomitantly. The downside of this approach is that health care in general changes over time; therefore, it could be that the results for hard cardiovascular disease outcomes are not only the consequence of the introduction of statins but also due to improvements in health care per se. Among the background population during this same time frame, studies have shown a decrease in mortality from cardiovascular disease over time but a mild increase in the prevalence of cardiovascular disease over time, findings that render the survival analysis for cardiovascular events even more striking.

Another potential point of concern is that the sensitivity of ultrasonographic examinations may affect results. The findings in previous studies involving this population that used the same standardized methods proved that carotid intima–media thickness, even in the thin arterial walls of young patients, could sufficiently describe small changes reproducibly in atherosclerosis progression, such that differences in carotid intima–media thickness between persons with familial hypercholesterolemia and unaffected siblings could be observed from a very early age.[3,9] In our current follow-up study, we made every effort to limit variability by using the same device, the same sonographer, and the same three image analysts to assess the same patients at each examination. Because the data analysis showed no significant differences between the two groups, we concluded that progression of carotid intima–media thickness in the affected, treated patients and unaffected, untreated siblings was similar. However, although the data on carotid intima–media thickness in our study are reassuring, further follow-up may show the extent to which the risk of cardiovascular disease is actually reduced over a lifetime. Therefore, we cannot presently draw definite conclusions about the predictive value of carotid intima–media thickness in patients with familial hypercholesterolemia in whom statin therapy was initiated early, nor can we consider the acceptance of targets for LDL cholesterol that are higher than the currently recommended targets.

The present prospective cohort study was conducted over a long period of time and could therefore be prone to participant attrition, which leads to loss of power and potentially introduces bias. However, data on vital status were obtained for all patients in the original cohort, and data on cardiovascular events were obtained for 95% of the cohort. Approximately 85% of our cohort had in-person follow-up visits as part of the present study. Because almost all the known reasons for nonparticipation were not associated with the presence of familial hypercholesterolemia or the outcome measures, we believe that the risk of attrition bias is small.

In conclusion, LDL cholesterol is considered a key factor in the pathway leading to atherosclerotic cardiovascular disease; therapy to decrease LDL cholesterol levels appears important in preventing or slowing its development. The results

of the present study showed that statins, initiated in childhood, slowed the progression of carotid intima–media thickness and reduced the risk of cardiovascular disease in adulthood.

Supported by a grant from the AMC Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the study participants; Johan Gort, B.Sc. (Amsterdam University Medical Centers, Department of Vascular Medicine), for performing all ultrasonographic measurements; Harry R. Büller, M.D., Ph.D. (Amsterdam University Medical Centers, Department of Vascular Medicine), for reading an earlier version of the manuscript and providing comments; and Marcel G.W. Dijkgraaf, Ph.D., and Aeilko H. Zwinderman, Ph.D. (both at Amsterdam University Medical Centers, Department of Clinical Epidemiology, Biostatistics, and Bioinformatics), for helping with the statistical analysis. None of the persons named received compensation for their contributions to the study.

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