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Long-term follow-up of young adults with familial hypercholesterolemia after participation in clinical trials during childhood

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BACKGROUND: There are little long-term data on patients with familial hypercholesterolemia (FH) who initiated lipid-lowering therapy during childhood.

OBJECTIVE: To study long-term outcomes in young adults with FH who participated in clinical trials on lipid-lowering therapy during childhood.

METHODS: Participants in at least 1 of 6 clinical trials that took place between 1999 and 2008 were interviewed in 2011 or 2013. Frequency of medical consultations, use of lipid-lowering therapy, lipid levels, side effects, diet, tobacco use, and emotional issues were investigated using information from interviews, blood samples and medical records.

RESULTS: Of the 118 individuals who participated in the trials, 67 (57%) were included. Median age was 25 years, and median time before follow-up was 10 years. Forty-eight (72%) participants were using statins at follow-up, 8 (12%) were also using ezetimibe, and 19 (28%) were not using any lipid-lowering therapy. Mean LDL-cholesterol (LDL-C) was 3.68 mmol/L in statin users and 6.08 mmol/L in non-users ($P < .001$). Only 6 (9%) participants reached treatment goal, ie, an LDL-C ≤2.5 mmol/L. Participants who attended a consultation ≤2 years before follow-up had a significantly lower LDL-C compared with those who had a consultation >2 years before follow-up (4.10 and 5.17 mmol/L, respectively; $P = .02$). Statin users had their last consultation more recently than non-users (median 1.4 and 2.2 years, respectively; $P = .02$).

CONCLUSIONS: Statins are underused in this population, and most patients have not reached treatment goal. Those with recent consultations had lower LDL-C levels and were more often statin users. Therefore, yearly consultations for young adults with FH seem warranted.

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Introduction

Familial hypercholesterolemia (FH) is an inherited, autosomal dominant disorder characterized by a reduced capacity to clear low-density lipoprotein (LDL) from the circulation, resulting in increased total cholesterol (TC) and LDL-cholesterol (LDL-C) levels in serum. Individuals with FH are predisposed to premature atherosclerosis and coronary heart disease (CHD). The vast majority of FH (85%–90%) is caused by defects in the LDL-receptor (LDL-R) gene, resulting in non-functioning or dysfunctioning LDL-Rs on the cell surface. Defects in the genes for apolipoprotein B (ApoB) and proprotein convertase subtilisin/kexin type 9 account for 5% to 10% and less than 5% of FH, respectively.[1] Heterozygous FH is common in Western populations, with an estimated incidence of 1 per 200 to 500 persons.[2–4] Early diagnosis and initiation of lipid-lowering therapy, primarily statins, are essential to prevent early CHD.[5,6]

Many randomized controlled clinical trials on statin treatment in children have been conducted since 1997, some lasting up to 2 years.[7–11] Statin treatment was well tolerated in these trials and did not affect growth or maturation, and these trials became the clinical basis for recommendations to consider statin treatment at 8 years of age.[3,12] However, long-term data on patients who initiated statin treatment in childhood are sparse.[13,14] Thus, here, we present the results of a follow-up study of long-term outcomes in young adults with FH who participated in clinical trials on different lipid-lowering therapies during childhood.

Material and methods

The Lipid Clinic at Oslo University Hospital has treated children and adults with FH for over 30 years. Between 1999 and 2008, the Lipid Clinic conducted 6 clinical trials on different lipid-lowering therapies in children under 18 years of age: 3 of them tested statin treatment, 1 tested statin treatment and ezetimibe, 1 tested colesevelam, and 1 tested plant sterol–enriched margarine. The 5 drug trials were multicenter,[8–10,15,16] and the plant sterol trial was a single-center trial, conducted only at the Lipid Clinic[17] (Table 1). All individuals who participated in 1 or more of these trials were eligible to participate in the present follow-up study.

There were 118 individuals who participated in the 6 trials, 8 of whom participated in 2 trials and one of whom participated in 3 trials. Data from the most recent trial were used for those who participated in more than 1 trial. We sent all 188 trial participants an invitation letter, informed consent form, and return envelope by mail, and after 1 to 2 weeks, all of them were contacted by phone. If contact was not achieved, repeated phone calls were made. Thirteen refused to participate, 33 could not be reached, and 5 were excluded as they did not have FH according to the criteria of the Dutch Lipid Clinic Network,[18] leaving 67 (57%) participants in the present follow-up study (Fig. 1). This study was approved by the regional ethics committee. Written informed consent was obtained from all participants.

Interviews were conducted with all participants by phone, or in person at the Lipid Clinic. Participants in trials 2 and 3 were interviewed in 2011, mostly by phone. Participants in trials 1, 4, 5, and 6 were interviewed between October 2013 and January 2014, mostly at the Lipid Clinic (Fig. 1). Most of those who were interviewed at the Lipid Clinic also underwent an optional physical examination, including measurements of height, weight, and blood pressure, which was measured using a Welch Allyn 5300 automated blood pressure device with the participant in a seated position, after 5 minutes of rest.

Interviews were done using a questionnaire developed by the authors of this article, in which all qualitative questions were either open ended or had a format with agree/disagree options on a 5-point scale ranging from strongly agree to strongly disagree. Information on FH diagnosis, CHD in parents and grandparents, frequency of medical consultations, use and dosage of past and current lipid-lowering therapy,

Table 1 Trials in children with FH from which the study population was taken

			Number of participants		
Trial	Lipid-lowering therapy	Year conducted	Total	Lipid Clinic	Included in follow-up study
Trial 1	Plant sterol[17]	1999–2000	41	41	13
Trial 2	Atorvastatin[9]	2000–2001	187	25	15
Trial 3	Simvastatin[8]	2000–2001	173	22	13
Trial 4	Colesevelam[15]	2006–2007	194	9	4
Trial 5	Ezetimibe/simvastatin[16]	2005–2007	248	8	4*,†
Trial 6	Rosuvastatin[10]	2006–2008	177	23	18†,‡
Total	—	—	1020	128/118§	67

FH, familial hypercholesterolemia.
*One person had also participated in 1 of the previous studies.
†For participants in more than 1 study, the last study participation was used.
‡Seven persons had also participated in 1 of the previous studies.
§Eight persons participated in 2 trials, and 1 participated in 3 trials, leaving 118 persons to be invited to the follow-up study.