ORIGINAL INVESTIGATION

Long-term Compliance With Lipid-Lowering Medication After Genetic Screening for Familial Hypercholesterolemia

Marina A. W. Umans-Eckenhausen, MD; Joep C. Defesche, PhD; Marjel J. van Dam, MD; John J. P. Kastelein, MD, PhD

Background: Familial hypercholesterolemia is a common lipid disorder that predisposes to premature cardiovascular disease. Lipid-lowering treatment of affected individuals is widely advocated, and maximum benefit can be obtained if medication is started early. A screening program for familial hypercholesterolemia is ongoing in the Netherlands since 1994. To assess the extent of treatment and therapy compliance, patients were followed up for 2 years after the diagnosis was established.

Methods: Data were obtained by questionnaire. The 747 patients with familial hypercholesterolemia participating in the study were from the general community, and 62.4% were not receiving cholesterol-lowering medication.

Results: The overall percentage of treated patients had risen from 37.6% at screening to 92.5% 1 year later and then decreased to 85.9% 2 years after screening. During follow-up, 6.4% of patients discontinued their medication and 12.0% of untreated patients never started medication for various reasons, but in the majority of cases as advised by their own physicians. The mean reduction in low-density lipoprotein cholesterol levels in previously untreated patients was 30.1% (from 219 to 153 mg/dL [5.7 to 4.0 mmol/L]).For those already receiving treatment, an additional reduction of 10.3% (from 195 to 175 mg/dL [5.0 to 4.5 mmol/L]) was obtained.

Conclusions: Most patients were receiving treatment 2 years after identification and had a positive attitude toward the screening program. However, the reduction of cholesterol levels still did not meet the internationally accepted goals of treatment. This underscores the fact that additional education is required to improve the treatment of individuals with familial hypercholesterolemia.

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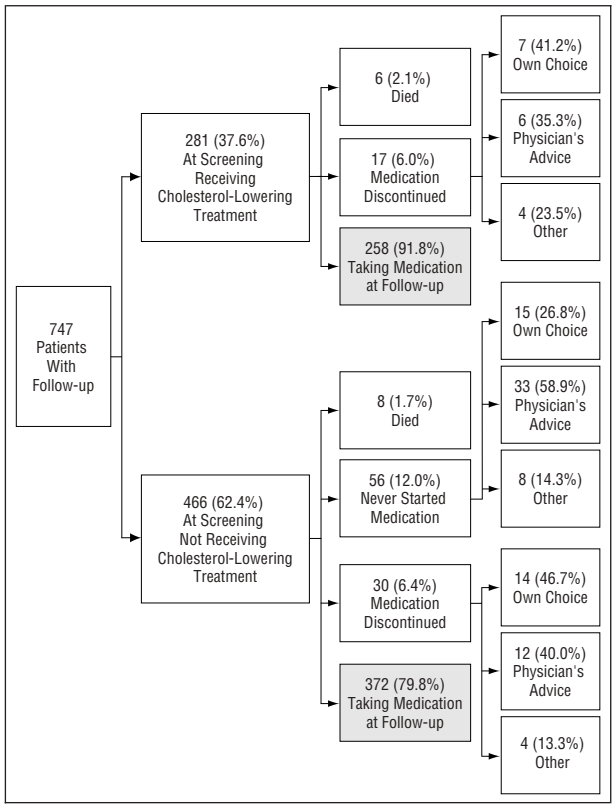
From the Foundation for the Identification of Persons With Inherited Hypercholesterolemia (Drs Umans-Eckenhausen and Kastelein), and the Department of Vascular Medicine, Academic Medical Center at the University of Amsterdam (Drs Umans-Eckenhausen, Defesche, van Dam, and Kastelein), Amsterdam, the Netherlands.

FAMILIAL hypercholesterolemia (FH) constitutes a common inherited disorder of lipoprotein metabolism with a prevalence of 1 in 400 to 500 persons in Western societies. The major risk conferred by FH is due to pronounced atherosclerosis leading to premature cardiovascular disease (CVD) and untimely death.[1] With the introduction of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), effective treatment of patients with FH has become feasible.[2,3] It has become evident that aggressive reduction of low-density lipoprotein (LDL) cholesterol levels in these patients can even lead to true regression of arterial wall abnormalities and that such a treatment is well tolerated and safe.[4,5] The identification and subsequent treatment of patients with FH have therefore become an important task in the prevention of CVD.

In 1994, a nationwide screening program for the identification of individuals with FH was instituted in the Netherlands.[6] The aim of this program is to identify patients with FH in the presymptomatic stage of the disorder, to offer them prophylactic therapy. The approach followed consisted of genealogic studies combined with DNA diagnostic testing in family members of patients with a proven mutation in the LDL-receptor gene. As reported earlier by our group, at the time of examination, approximately one third of adult patients with FH were receiving some form of cholesterol-lowering treatment, whereas 1 year later this percentage had risen considerably.[6]

The attainment of low LDL plasma levels often requires high-dose or combination drug therapy, which may be limited by poor tolerance.[7] In patients with FH, lifelong treatment with lipid-lowering drugs is indicated. Therefore, long-term appraisal of therapeutic goals is warranted to provide a more accurate assessment of the effectiveness of the program. We therefore performed a large-scale follow-up study 2 years after the diagnosis of FH was es-



Composition of the patient cohort studied and medication status of 747 patients with familial hypercholesterolemia after identification by DNA diagnosis. Because of rounding, percentages may not total 100.

tablished. Other important issues related to this family-based genetic testing program, such as genotype-phenotype relations, cost-effectiveness, and psychological and societal issues, are the subjects of separate reports.

METHODS

THE SCREENING PROGRAM

The screening program was executed as described previously.[6] Briefly, at a lipid clinic, part of a nationwide network, patients were diagnosed as having FH on clinical grounds according to a uniform diagnostic protocol.[8] DNA samples were analyzed for the presence of an LDL-receptor gene mutation. Once a functional mutation had been identified in such a patient, this patient was referred to as an index patient. Subsequently, first- and second-degree relatives of the index patient were actively contacted and tested for the mutation present in the index patient. Those shown to be carriers of the mutation were referred to a lipid clinic or advised to visit a specialist for further assessment of their cardiovascular risk, appropriate treatment, and instructions about preventive measures to reduce risk factors.

PARTICIPANTS AND INCLUSION CRITERIA

Consecutive participants in the program, in whom a DNA diagnosis of FH was established, were eligible for the follow-up study. A questionnaire was administered 2 years after the participants tested positively for the LDL-receptor mutation that caused FH in their family. Carriers younger than 18 years at the time of DNA testing were excluded from the study, since drug therapy in this age group is currently not established. Care was taken not to include many patients from the same family, to compose a study cohort representative of the total group of patients with FH identified in the program. Consenting participants received a letter explaining the purpose of the study and a questionnaire. In case of nonresponse, a reminder was sent within 1 month. If necessary, we sought to contact the participant through his or her relatives by telephone.

THE QUESTIONNAIRE

The questionnaire contained questions about type of treatment, diet, lifestyle, adverse effects of medication, and, if therapy had not been initiated or had been discontinued, what the reason was. In addition, the opinion and perceived value of the screening program were assessed. The questionnaires had a specific numbered code and could be returned anonymously.

STATISTICAL ANALYSIS

All data were analyzed with SPSS software (version 9.0; SPSS Inc, Chicago, Ill). Differences between baseline and 2-year plasma lipid and lipoprotein levels were tested with a paired *t* test.

RESULTS

PARTICIPATION

Between January 3, 1994, and January 30, 1998, 896 consecutive individuals (487 women and 409 men) were identified as carriers of an FH-causing mutation. Of these, 761 were older than 18 years. Nine (1.0%) did not consent and 5 (0.6%) were unavailable for follow-up. Complete 2-year follow-up was therefore obtained in 747 patients with FH (98.2%) (415 women and 332 men).

EFFECT ON THERAPEUTIC STATUS

The **Figure** gives an overview of the therapeutic status of the 747 patients with FH with complete follow-up after DNA diagnosis. At screening, 281 (37.6%) of the patients were already receiving cholesterol-lowering medication. This percentage rose to 92.5% after 1 year, but subsequently 14 FH carriers died and another 47 patients who were taking medication or stated medication after screening discontinued their medication during the course of follow-up. The proportion of patients taking lipid-lowering treatment 2 years after diagnosis had declined to 86.0% (630 of the 733 patients still living). The 47 patients discontinued the cholesterol-lowering medication because of disinterest and own choice (14 [29.8%]), adverse effects (7 [14.9%]), physician's advice (16 [34.0%]), wish to become pregnant or breastfeeding (8 [17.0%]), and unknown reasons (2 [4.3%]).

At screening, 466 patients (62.4%) were not receiving any cholesterol-lowering treatment, but 56 patients (7.5%) never started taking medication. Reasons for this were their own choice and disinterest (15 patients [26.8%]), being told by their primary care physician that it was unnecessary (33 [58.9%]), wish to become pregnant (4 [7.1%]), and unknown reasons (4 [7.1%]).

Patients who were still taking medication after 2 years received their prescription from their general practitioner (41.1%), internist (37.1%), or cardiologist (21.0%).

Lipoprotein Levels at Screening and 2 Years Later in Patients With FH With and Without Cholesterol-Lowering Medication at the Time of Diagnosis*

Receiving Cholesterol-Lowering Medication at Screening	No. of Patients	Lipoprotein	Mean (SD) Level, mg/dL		% Change
			At Screening	2 y After Screening	
No	183	Total cholesterol	298 (58)	230 (48)	–22.8
		Triglycerides	165 (88)	150 (79)	–9.1
		HDL cholesterol	44 (11)	47 (12)	+6.8
		LDL cholesterol	219 (58)	153 (58)	–30.1
Yes	118	Total cholesterol	274 (64)	249 (63)	–9.1
		Triglycerides	169 (136)	157 (117)	–7.1
		HDL cholesterol	45 (12)	46 (11)	+2.2
		LDL cholesterol	195 (60)	175 (56)	–10.3

Abbreviations: FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversion factors: To convert lipoprotein levels to millimoles per liter, multiply by 0.0259 for cholesterol and 0.0113 for triglycerides.
*P value (between levels at screening and after 2 years) was calculated by means of a paired t test. For all comparisons, $P<.001$.

EFFECT ON PLASMA LIPID AND LIPOPROTEINS

In the initial years of the program, DNA testing was combined with measurement of lipoprotein levels, but the latter was discontinued in the years thereafter. For this reason, the study cohort in which lipoprotein levels were assessed was smaller. The **Table** shows mean levels of total, LDL, and high-density lipoprotein (HDL) cholesterol and triglycerides at screening and follow-up of 183 patients with FH untreated at the time of screening. Mean total and LDL cholesterol and triglyceride levels fell by 22.8%, 30.1%, and 9.1%, respectively, while HDL cholesterol levels increased by 6.8%. All of these changes were statistically significant ($P<.001$). In addition, the Table shows the mean levels of total, LDL, and HDL cholesterol and triglycerides of 118 patients with FH who were taking cholesterol-lowering treatment at the time of screening and had continued medication for 2 years. The levels of total and LDL cholesterol and triglycerides decreased by an additional 9.1%, 10.3%, and 7.1%, respectively, whereas HDL cholesterol level increased by 2.2%. All changes were statistically significant ($P<.001$). Of all patients receiving treatment 2 years after the diagnosis was established, 66.0% achieved treatment target levels for LDL cholesterol of 135 mg/dL (3.5 mmol/L) or lower.

OPINIONS OF THE PARTICIPANTS

A total of 624 patients with FH (85.1%) reported a positive attitude toward the screening program, 95 (12.9%) expressed a neutral opinion, and 14 (1.9%) communicated a negative opinion and regretted the DNA testing.

COMMENT

Familial hypercholesterolemia represents the ideal paradigm for genetic testing, since effective medication for treatment of the disorder is widely available and effective therapy for FH can be easily assessed by measurement of lipoprotein levels and possibly by noninvasive imaging of the thickness of the intima-media complex of the carotid arteries.[5]

Patients with FH have a high risk for the development of CVD at a relatively young age, a risk that can be reduced by the timely institution of effective drug therapy. Still, many patients with FH are undiagnosed and lack the appropriate risk-reducing therapy.[9-11] Our group recently demonstrated that a DNA-based screening program was highly effective in identifying patients with FH.[6] Our current findings extend these observations and demonstrate that long-term adherence to therapeutic intervention is feasible and that a sharp reduction in cholesterol plasma levels was achieved.

Our study showed that, after identification through screening, the percentage of FH carriers treated with cholesterol-lowering medication exhibited a striking increase from 37.6% to 85.9% after 2 years. As could be expected, total and LDL cholesterol and triglyceride levels decreased and HDL cholesterol levels increased significantly in the previously untreated group of FH carriers. However, an improvement of the lipoprotein levels was also observed in patients who were already receiving cholesterol-lowering medication at the time of screening. These changes are likely to result in an important decrease in CVD risk. Various studies have demonstrated that a 1% reduction in LDL cholesterol level will lead to a decrease in CVD incidence of 1.0% to 1.7%.[12,13]

Mean baseline LDL cholesterol level was 219 mg/dL (5.7 mmol/L) but fell to 153 mg/dL (4.0 mmol/L) after 2 years, which represents a reduction of 30.1%. Therapeutic goals in these patients include a reduction of LDL cholesterol concentrations to less than 135 mg/dL (3.5 mmol/L) for primary prevention according to the European guidelines.[14,15] This treatment target was achieved by 66.0% of the patients, in both men and women. It is therefore evident that efforts should be directed toward more vigorous reduction of LDL cholesterol levels in these patients with FH.

Even in FH carriers who are already receiving cholesterol-lowering treatment, significant effects on plasma lipoprotein levels were observed after identification by DNA testing. Mean LDL cholesterol levels at the time of screening (195 mg/dL [5.0 mmol/L]) indicated that these patients were severely undertreated. After 2 years, these levels fell significantly to 175 mg/dL [4.5 mmol/L] but still did not reach the treatment target levels of 135 mg/dL [3.5 mmol/L] or lower.

The psychosocial consequences and the unavoidable breach of privacy caused by active genetic screening are widely discussed, often with a negative connotation. However, studies in families at risk for Huntington disease or hereditary breast cancer have, as yet, shown little evidence of significant psychological suffering as a result of genetic testing.[16] It is noteworthy that in the present study, under anonymous conditions, a high percentage of FH carriers (85.1%) had a positive attitude, whereas only 1.9% expressed a negative experience with the program. Data on the percentage of participants who regretted predictive testing afterward, except for the multiple endocrine neoplasia type 2 syndrome (5%) and cystic fibrosis (10%-12%), are sparse but do not seem to indicate major dissatisfaction.[17-19]

Recently, Marteau and Lerman[20] reported that behavioral change after identification of a genetic risk was difficult to achieve. In contrast, the results of our survey, such as the significant increase in treatment levels and the overall positive attitude toward the screening program, do not support their findings. Indeed, 103 (14.1%) of 733 patients still living at the time of the follow-up study discontinued or never initiated medication, but the decision to do so was mainly based on general disinterest or on advice of the treating physician. This indicates that, for this relatively small group of patients and their treating physicians, additional education is required.

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Corresponding author and reprints: Joep C. Defesche, PhD, Department of Vascular Medicine, G1-112B, Academic Medical Center, University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, the Netherlands (e-mail: j.defesche@amc.uva.nl).

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