Genetic insights, clinical efficacy and practical implications of genetic screening for familial hypercholesterolemia
Umans-Eckenhausen, M.A.W.

Citation for published version (APA):
Chapter 5

Long-term compliance to lipid lowering medication after genetic screening for Familial Hypercholesterolemia

Marina A.W. Umans-Eckenhausen¹,², Joep C. Defesche², Marjel J. van Dam² and John J.P. Kastelein¹,²

¹ Foundation for the Identification of Persons with Inherited Hypercholesterolemia
Paasheuvelweg 15, 1105 BE Amsterdam, The Netherlands

² Department of Vascular Medicine, Academic Medical Center at the University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, The Netherlands

Arch Intern Med 2002 (in press)
Abstract

Introduction
Familial Hypercholesterolemia (FH) is a common lipid disorder that predisposes for premature cardiovascular disease. Lipid-lowering treatment of affected individuals is widely advocated and maximum benefit can be obtained if medication is started early. A DNA- and family based screening program for Familial Hypercholesterolemia is ongoing in the Netherlands since 1994. In order to assess the extent of treatment and therapy compliance, patients were followed up for two years, after the diagnosis was established.

Methods
Data were obtained by a questionnaire survey.

Results
The 747 patients with FH, participating in the study, were from the general community. Of these 62.4% were not receiving cholesterol-lowering medication. The overall percentage of treated patients had risen from 37.6% at screening up to 92.5% one year later and then slightly decreased to 86% 2 years after screening. During follow-up, 6% of all patients discontinued their medication and 12% of untreated patients never started medication for various reasons, but unfortunately in the majority of cases as advised by their own physicians. The mean reduction in LDL-cholesterol levels in previously untreated patients was 30% (from 219 to 153 mg/dl), while for those already on treatment, an additional reduction of 12% (from 195 to 175 mg/dl) was obtained in the course of the program.

Discussion
The results of our survey indicate that the vast majority of patients was on treatment two years after identification and had a positive attitude towards the screening program. However, the reduction of cholesterol levels still did not meet the nationally and internationally accepted goals of treatment. This underscores the fact that additional education is required to improve the treatment of individuals with Familial Hypercholesterolemia.
Introduction

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. With the introduction of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), effective treatment for FH patients has become feasible. 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. The identification and subsequent treatment of FH patients has therefore become an important task in the prevention of CVD.

In 1994, a nation-wide screening program for the identification of individuals with FH has been instituted in the Netherlands. The aim of this program is to identify FH patients in the pre-symptomatic stage of the disorder, in order to offer them prophylactic therapy. The approach followed consisted of genealogical studies combined with DNA diagnostic testing in family members of patients with a proven mutation in the LDL-receptor gene. As we reported earlier, at the time of examination approximately one third of adult FH patients were receiving some form of cholesterol-lowering treatment, whereas one year later this percentage had risen considerably.

The attainment of low LDL plasma levels often requires high dose or combination drug therapy, which may be limited by poor tolerance. 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 two years after the diagnosis FH had been established. Other important issues related to this family-based genetic testing program, such as genotype-phenotype relations, costs-effectiveness and psychological and societal issues, is the subject of separate reports.

Methods

The screening program
The screening program was executed as described previously. Briefly: at a Lipid Clinic, part of nation-wide network, patients were diagnosed with FH on clinical grounds,
according to a uniform diagnostic protocol. DNA samples were analyzed for the presence of a LDL-receptor gene mutation. Once a functional mutation had been identified in such a patient, this patient was referred to as an index case. Subsequently, first and second-degree relatives of the index patient were actively contacted and tested for the mutation present in the index case. Those shown to be carrier 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 of the program, in whom a DNA diagnosis of FH was established, were eligible for the follow-up study. A questionnaire was administered two years after the participants were 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, in order to compose a study cohort representative for the total group of FH patients identified in the program. Consenting participants received a letter explaining the purpose of the study and a questionnaire. In case of non-response a reminder was sent within one month. If necessary, we sought to contact the participant through their relatives by telephone.

The questionnaire
The questionnaire contained questions about type of treatment, diet, life style, adverse effects of medication and in case 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 using SPSS software (version 9.0, SPSS, Chicago, USA). Differences between baseline and two years plasma lipid and lipoprotein levels were tested using a paired Student’s t-test.
Long-term compliance to medication

**Results**

**Participation**

In the period between January 1994 and January 1998, 896 consecutive individuals (487 women, 409 men) were identified as carriers of a FH causing mutation. Of these, 761 were older than 18 years. Nine (1.1%) did not consent and 5 (0.7%) were lost to follow-up. Complete two-year follow-up was therefore obtained in 747 (98.2%) FH patients (415 women and 332 men).

**Figure 1. Composition of the patient cohort studied and medication status of 747 FH patients after identification by DNA diagnosis.**

**Effect on therapeutic status**

In figure 1 an overview is given of the therapeutic status of the 747 FH patients with complete follow-up after DNA diagnosis. At screening, 281 (37.6%) of the patients were already receiving cholesterol-lowering medication. This percentage had risen to 92.5% after one year, but subsequently 14 FH carriers died and another 47 discontinued their medication. The proportion of patients on lipid lowering treatment, two-years after diagnosis, declined to 86.0% (630 out of the still living 733). The 47 patients discontinued the cholesterol lowering medication because of disinterest and own choice (29.8%),
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adverse effects (14.9%), doctor's advice (34%), pregnancy (wish) or breast feeding (17.0%) and while 2 patients stopped for unknown reasons (4.3%). At screening 466 (62.4%) patients were not receiving any cholesterol lowering treatment, but 56 patients (7.5%) never were initiated on medication because of. Reasons for this were: own choice and disinterest (26.8%), not necessary according to primary care physician (58.9%), pregnancy (wish) (7.1%) or unknown reasons (7.1%). Patients who were still on medication after two years received their prescription from their general practitioner (41%), internist (37%) or cardiologist (21%).

**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. In Table 1 mean levels of total-, LDL-, HDL-cholesterol and triglycerides at screening and follow up, of 183 FH patients untreated at the time of screening, are presented. Mean total-, LDL-cholesterol and triglyceride levels fell by 23%, 30% and 9% respectively while HDL-cholesterol increased by 6%. All these changes were statistically significant (P<0.0001). Additionally, Table 1 also shows the mean levels of total-, LDL -and HDL cholesterol and triglycerides of 118 FH patients that were on cholesterol lowering treatment at time

<table>
<thead>
<tr>
<th>receiving cholesterol lowering medication at screening</th>
<th>N</th>
<th>at screening*</th>
<th>2 years after screening*</th>
<th>% change</th>
<th>P-value*</th>
</tr>
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<tbody>
<tr>
<td>No</td>
<td>183</td>
<td>298 (58)</td>
<td>230 (48)</td>
<td>-22.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>165 (88)</td>
<td>150 (79)</td>
<td>-9.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 (11)</td>
<td>47 (12)</td>
<td>+6.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>219 (58)</td>
<td>153 (58)</td>
<td>-30.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>118</td>
<td>274 (64)</td>
<td>249 (63)</td>
<td>-9.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>169 (136)</td>
<td>157 (117)</td>
<td>-7.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 (12)</td>
<td>46 (11)</td>
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<td>195 (60)</td>
<td>175 (56)</td>
<td>-10.2</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

P-value (between levels at screening and after 2 years) was calculated using a paired Student t-test; N: number of patients; s.d.: standard deviation; LDL: low-density lipoprotein; HDL: high-density lipoprotein. To convert lipoprotein levels from mg/dl to mmol/l, divide by 38.6 for cholesterol and by 88.5 for triglycerides. * = Mean (standard deviation) in mg/dl.

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of screening and had continued medication during two years. The levels of total- and LDL-cholesterol and triglycerides decreased by an additional 8%, 12% and 6%, respectively, whereas HDL-cholesterol increased by 3%. All changes were statistically significant (P<0.0001). Of all patients on treatment two years after the diagnosis was established, 66% achieved treatment target levels for LDL-cholesterol of 135 mg/dl or lower.

**Opinion of the participants**

A total of 624 FH patients (85%) reported a positive attitude towards the screening program, 95 (13%) expressed a neutral opinion and 14 (2%) communicated a negative opinion and regretted the DNA testing.

**Discussion**

FH 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 non-invasive imaging of the thickness of the intima-media complex of the carotid arteries.\(^5\)

FH patients have a high risk for the development of cardiovascular disease at a relative young age; a risk that can be reduced by the timely institution of effective drug therapy. Still many FH patients suffer from under-diagnosis and lack the appropriate risk reducing therapy.\(^9\)\(^-\)\(^11\) We 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 following identification through screening, the percentage of FH carriers treated with cholesterol lowering medication exhibited a striking increase from 38% to 86% after 2 years. As could be expected, total and LDL cholesterol and triglyceride levels decreased and HDL cholesterol increased significantly in the previously untreated group of FH carriers. But also in patients that were already receiving cholesterol-lowering medication at the time of screening, an improvement of the lipoprotein levels was observed. These changes are likely to result in an important decrease of CVD risk. Various studies have demonstrated that a 1% reduction of LDL cholesterol will lead to a decrease in CVD incidence of 1 to 1.7%.\(^12\)\(^,\)\(^13\)

Mean baseline LDL-cholesterol levels were 219 mg/dl but fell to 153 mg/dl after two
years, which represents a reduction of 30.1%. Therapeutic goals in these patients include a reduction of LDL-cholesterol concentrations to less than 135mg/dl for primary prevention according to the European guidelines.\textsuperscript{14,15} This treatment target was achieved 66% of the patients, both in men and women. It is therefore evident that efforts should be directed towards more vigorous reduction of LDL-cholesterol levels in these FH patients. Even in FH carriers already receiving cholesterol-lowering treatment, significant effects on plasma lipoproteins were observed after identification by DNA-testing. Mean LDL-cholesterol levels at the time of screening (195 mg/dl) indicated that these patients were severely under-treated. After two years these levels fell significantly to 175 mg/dl, but still did not reach the treatment target levels of 135 mg/dl or lower.

The psychosocial consequences and the unavoidable breach of privacy caused by active genetic screening are widely discussed and often with a negative connotation. However studies in families at risk for Huntington’s disease or hereditary breast cancer have, as yet, shown little evidence of significant psychological suffering as a result of genetic testing.\textsuperscript{16} It is noteworthy that in the present study, under anonymous conditions, a high percentage of FH carriers (85%) had a positive attitude, whereas only 2% expressed a negative experience with the program. Data on the percentage of participants that regretted predictive testing afterwards, except for the MEN-2 syndrome (5%) and for cystic fibrosis (10-12%), is sparse but do no seem to indicate major dissatisfaction.\textsuperscript{17-19}

Recently, Marteau and Lerman reported that behavioral change after identification of a genetic risk was difficult to achieve.\textsuperscript{20} In contrast, the results of our survey, such as the significant increase in treatment levels and the overall positive attitude towards the screening program, do not support their findings. Indeed, 103 of 733 patients (14%) 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.

**Acknowledgements**

The authors gratefully acknowledge the contribution of the physicians of all Dutch Lipid Clinics by submitting blood samples of FH patients. This work was supported by grants of the Dutch Ministry of Public Health, Welfare and Sport, the Health Care Insurance Council and the Netherlands Heart Foundation.
References


