Genetic insights, clinical efficacy and practical implications of genetic screening for familial hypercholesterolemia
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Citation for published version (APA):

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Introduction and overview of this thesis
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In the Netherlands, a genetic screening programme for Familial Hypercholesterolemia (FH) was started in 1994. Two independent developments in FH research cleared the way for such a screening programme. These were the elucidation of diagnostic tools for the detection of the genetic defects underlying FH and the simultaneous breakthrough in the treatment of FH with the introduction of effective lipid lowering medication (HMG CoA reductase inhibitors).

Familial Hypercholesterolaemia is an inherited disorder of lipoprotein metabolism caused by mutations in the LDL-receptor gene. In heterozygous FH, only 50% of these receptors are functional, which increases plasma cholesterol concentrations to between 7-5 and 16 mmol/L.¹ In Europe, around 1 in 500 individuals are affected by the heterozygous form of the disease, making it the most common potentially lethal genetic disorder. A survey in 4 general practices in the Netherlands indicated that FH has a frequency of at least 1 in every 400 inhabitants.² The clinical hallmark of FH is the presence of xanthomata, deposits of cholesterol commonly seen in the Achilles tendon and in the extensor tendons on the back of the hands. These can appear by the end of the second decade, and by the third decade will be present in about half of all heterozygotes. However, the most important clinical feature of FH is the development of premature and extensive atherosclerosis leading to coronary heart disease (CHD) and untimely death.¹ In patients with FH the age- and sex-standardised mortality ratios are four to five times higher than in the general population and as a result, life expectancy in FH patients is reduced with 10-20 years.³ For the diagnosis, physicians rely largely on clinical criteria, such as tendon xanthomata, corneal arcus, family or personal history of early onset CHD and biochemical parameters such as plasma LDL-C levels.⁴ Various diagnostic approaches have been developed to assess the diagnostic criteria in each hypercholesterolemic patient in whom FH is suspected.⁵⁶ Still, many FH patients remain unrecognized.⁷⁸ This is especially true for younger FH patients in whom the classical symptoms of the disease have not been become apparent yet.⁹ With the elucidation of the molecular basis of this disorder, an unequivocal diagnosis has become available, even in the presymptomatic stage.

Over the past decade, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have become invaluable in the treatment of hypercholesterolemia.¹⁰
Several statin landmark trials showed that a reduction of LDL-cholesterol decreased the rate of major cardiovascular events (MACE), cardiac deaths and non-fatal myocardial infarctions, both in primary and secondary prevention.\textsuperscript{11,12,13,14,15,16} Patients with FH are at very high risk and it was shown recently that aggressive lipid lowering treatment even leads to regression of disease.\textsuperscript{17,18}

Considering that FH poses a serious health risk if neither recognised nor treated, given that adequate and acceptable diagnostic tools exist, and that there are proven, effective therapeutic interventions available, an active screening programme for FH clearly meets the most important, internationally accepted, criteria of Wilson and Junger for population screening programmes. In 1990 the Dutch Health Council concluded that: "Those with an inherited form of hypercholesterolemia would benefit from early identification and timely treatment and screening is recommended".\textsuperscript{19} Various international organizations, like the European Society of Cardiology and the World Health Organization (WHO) also called for active screening for FH.\textsuperscript{7,20}

Different forms and strategies for such an identification/screening programme can be developed. Two independent variables in this respect are:
- Low risk strategy (general population) versus high risk strategy (confined to FH families)
- Biochemical (lipid profile) method versus genetic (DNA testing) method.

By combining the two aforementioned variables, theoretically 4 different screening scenarios could be designed, each with advantages and disadvantages. The low risk strategy efforts remain impractical (DNA method) and ineffective (cholesterol measurements). Several initiatives have established the usefulness of targeting relatives of FH patients for identifying previously undetected cases using cholesterol testing.\textsuperscript{21,22} With this method in high risk families only 50% of the expected number of family members with hyperlipidemia could be identified in a Dutch study.\textsuperscript{23}

Therefore, in 1994 the initiative was taken by the Lipid Research Clinic of the University of Amsterdam to initiate a screening programme using DNA analysis as a screening instrument in relatives of FH patients in whom a DNA diagnosis was established.
The advantages postulated of DNA testing over cholesterol measurements as the screening instrument in FH are:

1. A DNA test would yield a higher sensitivity and specificity.
2. A single DNA test is sufficient for a diagnosis.
3. A DNA test is a simple blood test and will not be influenced by external factors, such as circadian patterns or nutritional status.

Possible disadvantages of the DNA test as compared to cholesterol could be:

1. Lower acceptance of the testing instrument by the population targeted.
2. Ethical dilemma’s (for example with respect to privacy aspects and possible violation of the right ‘not to know’ etc.)

The central topic of this thesis is the assessment of the genetic screening programme for FH with respect to the issues mentioned above. This thesis is based on the results, efforts and experience obtained in the Dutch Screening Programme for FH. This nation-wide screening programme is executed by the Stichting Opsporing Erfelijk Hypercholesterolemie (StOEH) since 1994 with financial support of the Ministry of Public Health, Welfare and Sport, the Health Care Insurance Council and the Dutch Heart Foundation.

**Part 1** describes the rationale for a genetic screening programme for FH. In particular, the concept of genetic screening in combination with active family investigation is introduced. In *chapter one* an overview of the various mutations in the LDL receptor gene in the Dutch population is given. To date worldwide more that 600 different mutations in the LDL-receptor gene have been identified. The molecular basis of the screening depends entirely upon the capability of the DNA laboratory to detect and to test new mutations for functionality and to categorize the various mutations found in the different families and regions in the country. In *chapter two* the relation between genotype and phenotype of the most common mutations found in the Netherlands are compared and evaluated with regard to lipoprotein levels and the cardiovascular risk. In *chapter three* the results of the first 5 years of the (experimental) nation-wide genetic screening programme
of FH are described. In this chapter also a comparison is made between the classical screening tool, measurement of cholesterol levels, and the new screening tool, DNA testing.

In the last chapter of part I (chapter 4), an overview is given of the current state of the identification, treatment and treatment options for FH. It ends with a summary of the advantages of early screening followed by timely treatment of FH patients.

In Part II of this thesis the different aspects of the clinical efficacy of FH screening and treatment are addressed. Chapter 5 describes the follow-up of the patients that were identified through the genetic screening programme described in chapter 3. In order to assess the value of a screening programme it is important to follow-up on the patients identified, since 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. Furthermore follow-up is required to assess the effect of such a programme on clinical outcome. Is the CVD risk reduced indeed and to which extent? This chapter focused on the two-years follow-up: assessment of therapy compliance, effects of therapy on lipid profiles and clinical events (cardiovascular events, death). Additionally, the attitude of the FH patients was assessed with regard towards the genetic screening programme.

The attainment of low LDL plasma levels often requires high dose or combination drug therapy, which may be limited by poor tolerance. Higher and higher doses are being used in order to obtain the therapeutic goals in the treatment of FH patients. The efficacy and the safety of a new high dose treatment with simvastatin 80 mg once daily was studied in a cohort of FH patients that visited the Amsterdam Lipid Clinics in the Academic Medical Center and in Slotervaart Hospital. These data are presented in chapter 6.

In chapter 7 the cost effectiveness of the Dutch screening programme is calculated. This study was a unique collaboration with a London study group; well known for their expertise in cost effectiveness studies in different FH screening models. 25

Part III is dedicated to the practical implications of this genetic screening programme for FH. One of the issues raised screening for FH appeared to be the genetic screening of minors. The benefits of screening and treatment of children with FH are currently under debate. However, the guidelines for genetic screening programmes still exclude children under 16. The dilemmas associated with genetic testing for adult-onset diseases in childhood, have lead experts to conclude that “not to know” should prevail and that
individuals should only be tested when they can decide for themselves. Chapter 8 focuses on parental attitudes towards genetic testing for FH in children and the factors that might influence their decision to have their own children tested are studied.

It is expected that in the near future similar predictive genetic screening programmes will be developed. Substantial knowledge and experience has been gathered by the screening organisation itself that can be useful for the development of such screening programmes. Important issues in this respect that still need to be resolved are: psychological and social effects (employment and insurance), cost-benefit analyses, ethical and juridical dilemmas and finally health benefits for the individual as well as for the population. These issues, finally, are being addressed in chapter 9.

References


19. Gezondheidsraad 1990/11: Cholesterol


24. www.vcl.ac.uk/fh