Genetic insights, clinical efficacy and practical implications of genetic screening for familial hypercholesterolemia
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Chapter 10

Summary
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This thesis summarizes the genetic insights, clinical efficacy and practical implications of the genetic screening programme for Familial Hypercholesterolemia in the Netherlands. This ongoing nation-wide screening programme was initiated in 1994 and has since been executed by the Foundation for the Identification of Persons with Inherited Hypercholesterolaemia (StOEH). The aim of this programme is to identify FH patients in the presymptomatic stage of the disorder in order to provide them with therapy. The ultimate goal is timely and effective lipid lowering treatment to reduce the cardiovascular burden of FH patients. The basis of the screening programme consists of DNA analysis in combination with pedigree based family investigation.

Part 1 describes the rationale for our genetic screening programme for FH. In particular, the concept of genetic screening in combination with active family investigation is introduced. In Part II of this thesis the different aspects of the clinical efficacy of FH screening and treatment are addressed. Part III is dedicated to the practical implications of the screening programme.

Part 1: Genetic insights

Familial hypercholesterolaemia (FH) is a genetic disorder that results from defects in a cell surface receptor for low-density lipoprotein (LDL), the major cholesterol transport particle in human plasma. In Europe, around 1 in 500 individuals is affected by the heterozygous form of the disease, making it the most common potentially lethal genetic disorder. These individuals produce approximately half the normal number of LDL receptors and LDL-cholesterol (LDL-C) is removed from the circulation at half the normal rate, resulting in LDL-C levels that are increased two- to three-fold (9–14 mmol/l). The homozygous condition is much less common, occurring with a frequency of approximately one in a million; LDL-C levels in homozygotes can be increased six- to ten-fold above normal.

Mutations in the LDL receptor gene are responsible for familial hypercholesterolemia (FH). In chapter one an overview of the various mutations in the LDL receptor gene in the Dutch population is given. Mutation analysis by Denaturing Gradient Gel Electrophoresis (DGGE) and sequencing in 1641 clinically diagnosed FH patients resulted in the
characterization of 159 LDL-receptor gene defects. The nine most common mutations were responsible for 66.5% of our FH index cases. Of these, four mutations occurred with relatively high frequencies in specific parts of the Netherlands. The remaining mutations were only encountered in single FH patients, comprising 22.2% of the patient cohort analysed. At present, more than 600 mutations in this gene are known to underlie FH. However, the array of mutations varies considerably in different populations. Therefore, the delineation of essentially all LDL-receptor gene mutations in a population is a prerequisite for the implementation of nation-wide genetic testing for FH.

Since the elucidation of the cholesterol pathway by Brown and Goldstein, many studies have addressed the relation between the mutation causing FH and the resulting phenotypic expression of the disorder. In chapter 2 an analysis and evaluation of the effect of different mutations in the LDL receptor gene on the lipoprotein levels and on cardiovascular (CVD) risk is being described. In previous studies, it was not clear whether variance of lipoprotein levels and CVD risk could be attributed to variation at the LDL-receptor locus or to other familial factors. Therefore, the exact relationship between the different LDL-receptor mutation classes, lipoprotein levels and the risk of CVD remained unclear. The Dutch national screening programme for FH provided, after exclusion of the index families, a unique cohort to study this genotype-phenotype relationship free from selection bias for CVD. A significant variation in mean LDL levels was observed in 399 FH patients with different mutations. The type of mutation did not influence high-density lipoprotein (HDL) cholesterol levels. FH patients had 8.5 times more often CVD compared to their unaffected relatives (RR 8.54, 95% CI 5.29-13.80), but CVD risk showed a large variation among the different types of mutations. The N543H/2393del9 mutation was associated with a smaller increase in risk compared to the other ‘non-null allele’ mutations (P < 0.0001). After exclusion of families with the N543H/2393del9 mutation, null alleles and other alleles mutations did no longer differ with regard to LDL cholesterol levels and CVD risk. It was concluded that LDL-receptor mutations can only partly explain the variation in LDL cholesterol levels and the cardiovascular burden of FH. Additional (so far unidentified) familial risk factors also contributed significantly to the CVD risk, independent of lipids and lipoproteins.

In chapter three the results of the first 5 years of the (experimental) nation-wide genetic screening programme of FH are described. In the first 5 years, 5442 relatives of 237
people with familial hypercholesterolaemia were screened; 2039 individuals were identified as heterozygous by LDL-receptor gene mutation analysis. On average, about 20 relatives of one index case could be traced, of which 8 (37%) were diagnosed by their carrier status. Targeted family screening with DNA analysis proved to be highly effective in identifying patients with hypercholesterolaemia. Most of the identified patients sought treatment and were successfully started on cholesterol-lowering treatment to lower the risk of premature CVD. Furthermore, we showed that familial hypercholesterolaemia is frequently underdiagnosed and that many patients who had been identified previously on clinical grounds were not being treated appropriately. Ten percent of possible participants declined genetic testing, mainly out of fear for social consequences, such as negative effects with regard to employment and insurance. In this chapter a comparison is also made between the classical screening tool, measurement of cholesterol levels, and the new screening tool, DNA testing. Laboratory analysis showed that for carriers as well as non-carriers 18% would have been misdiagnosed by cholesterol measurement alone, with sex-specific and age-specific 90th percentiles of the general Dutch population as diagnostic criteria.

In the last chapter of part I (chapter 4), an overview is given of the current state of the identification and treatment options for FH. It is reasoned that the early diagnosis of FH is extremely important, given the high risk of premature CVD even in the absence of other risk factors and that DNA-based test for FH is the most definitive tool for diagnosis and family tracing. The challenge of treating patients with FH is to prevent them developing premature coronary atherosclerosis. Statins are considered the first-line therapy for reducing LDL-C levels, because they are efficacious and well tolerated, and their use has been proven to reduce cardiovascular morbidity and mortality. Again, it is shown that there is clear evidence that the condition remains underdiagnosed. This chapter ends with the recommendation that since the success of targeted screening programmes in identifying new cases of FH has been established, it is now the responsibility of governments and health ministries to implement such programmes on a wider scale.
Part II: Clinical efficacy

With the introduction of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), effective treatment for FH patients has become feasible. Moreover, 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. In patients with FH, lifelong treatment with lipid lowering drugs is indicated. The attainment of low LDL plasma levels often requires high dose or combination drug therapy, which may be limited by poor tolerance. Therefore long-term appraisal of therapeutic goals is warranted to provide a more accurate assessment of the effectiveness of the nation wide genetic screening program. We therefore performed a large-scale follow-up study two years after the diagnosis FH had been established.

This study is described in chapter 5 of this thesis. 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 this occurred on advice of their own physician. 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. The results of this survey indicated that the vast majority of patients was on treatment two years after identification and had a positive attitude towards the screening programme. However, the reduction of cholesterol levels still did not meet the nationally and internationally accepted goals of treatment.

Clinical data suggesting that larger decreases in LDL-C result in greater reductions in CVD events have led to the establishment of aggressive LDL-C targets for the treatment of hypercholesterolemia. Therefore, the use of the highest registered dose of statins has increased considerably, notably in patients at the highest risk. However, data on the efficacy and safety of such doses in an uncontrolled out-patient setting are scarce. In chapter 6 we evaluate the efficacy and the safety of the maximum dose of simvastatin, 80 mg, in patients with FH. In a retrospective cohort study we reviewed the data on 74
consecutive FH patients, referred to the University Lipid Research Clinic in Amsterdam after at least 3 months therapy with simvastatin 80mg. It appeared that in this non-controlled outpatient setting, simvastatin 80mg was well tolerated and produced sharp reductions in LDL-cholesterol, total cholesterol and triglycerides, and significant elevations of HDL-C. However, these lipoprotein changes were smaller than those reported in randomized controlled trials with the same dose of the drug, suggesting less compliance even in this very high risk category of patients.

An assessment of the cost-effectiveness of a large-scale screening programme is important. Such a screening programme should be supported by public funding, if it is good value for money. We report an analysis of the costs and effects of the ongoing genetic screening programme in chapter 7. 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. Actual data from the screening programme from the year 2000 was used for total expenditure, numbers screened and carrier status and medication status of those screened. The data from the screening programme were supplemented by data from the Simon Broome Registry (UK). A cost-effectiveness analysis of the Dutch genetic screening programme for familial hypercholesterolaemia revealed an estimated cost of 8,700 euros per life-year gained. This represents good value for money when compared to a number of publicly funded health care interventions. The results were robust to changes in the model parameters. It was concluded that on the basis of the best available evidence, genetic screening of relatives of patients known to have heterozygous FH appears to be highly cost-effective. However, health gain would be optimized if after screening more patients were prescribed those statin regimens that have been shown to be more effective.
Part III: Practical implications

This part 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. Information on the attitudes of parents was not available with regard to genetic testing for FH in their children. Gender, carrier status, educational level and religion are known to influence the attitude towards genetic screening for other diseases in children. We choose to work with a decision model based on these four factors information, experience, expectation and emotion. The aim of the study in chapter 8 was to assess parental attitudes towards genetic testing for FH in children and to investigate the factors that might influence their decision. This study shows that 87.1% of parents from FH families wanted their children to undergo a genetic test. This is in contrast to the opinion of ethical experts that children should not be included in genetic screening programmes. Most parents found information the most important factor in the decision-making process. However, in the multivariate analysis it became evident that emotion actually was the only predictive factor and that factors information, experience and expectation did not show a significant relationship with the decision to test. These data indicate that the decision is based less on rationality then parents wish to believe.

This innovative screening programme for FH can serve as an example for genetic screening for other disorders in the population at large. It is expected that in the near future similar predictive genetic screening programmes will be developed. In anticipation of these future developments, it is important to evaluate all aspects of the current FH screening programme. Especially the bottlenecks, experienced throughout the years, are valuable and can serve as a teaching base for those that are engaged in prevention, patient care, or insurance and from a general policy perspective. These issues, finally, are being addressed in chapter 9. This chapter ends with the conclusion that in the field of genetic screening in the Netherlands much has been achieved. Still, there are a number of bottlenecks such as: the lack of structural financing of genetic screening programmes, the lack of quality assurance and auditing of genetic population screening. Furthermore, it is noted that, as a result of genetic screening, individuals do experience problems with insurances. These bottlenecks currently impairing the execution of genetic screening programmes have to be resolved in the nearby future.