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Summary

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In **chapter 2**, the clinical data are described of a very large cohort of children with Familial Hypercholesterolemia (FH). This chapter provides all the characteristics with regard to physical stigmata and lipoprotein abnormalities of childhood FH. In these children, the risk factors and their relation with cardiovascular disease (CVD) in the families are assessed. The latter could be of practical clinical relevance, since it might allow the timely identification of the children with FH who are at highest risk of CVD.

Elevated LDL cholesterol (LDL-C) levels in childhood predict CVD later in life. FH represents the paradigm of this relation. The objectives of the study described in this chapter were to (1) establish the LDL-C level that provides the most accurate diagnosis of FH in children from families with known FH and (2) assess whether lipoprotein variation in these children is associated with premature CVD in relatives. Foremost, however, it was our objective to identify children with FH who are at high risk and in need of early intervention. A total of 1034 consecutive children from FH kindreds were investigated. First, LDL-C levels > 3.50 mmol/L had a high post-test probability (98%) of predicting the presence of an LDL receptor mutation. Second, children with FH in the upper LDL-C tertile (> 6.23 mmol/L) had a 1.7-times higher incidence of having a parent with FH suffering from premature CVD then the lower tertiles. In addition, such a parent was found 1.8 times more often among children with FH having HDL cholesterol (HDL-C) < 1.00 mmol/L. Last, children with FH whose lipoprotein (a) was > 300 mg/L had a 1.5 times higher incidence of having a parent with FH suffering from premature CVD.

So, in children with heterozygous FH, physical characteristics are typical but rare. In those families in which the diagnosis of FH is certain, LDL-C levels allow accurate diagnosis of FH in their children. Moreover, increased LDL-C and lipoprotein (a) and decreased HDL-C levels in children identify FH kindreds with the highest CVD risk.

Chapter 3 describes the search into substantial variation of LDL-C levels in children with FH, by studying phenotype in 450 unrelated children with FH and in 154 affected sib-pairs, to avoid family bias. In previous studies, family members of children with FH were included, which may have influenced results. In known families with classical FH, diagnosis was based on plasma LDL-C above the age- and gender-specific 95th percentile.

Girls had higher LDL-C, compared with boys. Also in girls, HDL-C increased by age; this age effect was not observed in boys. The distribution of apolipoprotein (apo) E genotypes was not significantly different between probands, their paired affected siblings, or a Dutch control population. Carriers with or without one e4 allele had similar LDL-C and HDL-C levels. Within the affected sib-pairs, the e4 allele explained almost all of the variation of HDL-C levels (-0.15 mmol/L). The effect of

apoE4 on HDL-C differed with an analysis based on probands or on affected sib-pairs. The affected sib-pair model uses adjustment for shared environment, type of LDL receptor gene mutation, and a proportion of additional genetic factors and may, therefore, be more accurate in estimating effects of risk factors on complex traits. We therefore conclude that the e4 allele was associated with lower HDL-C levels in an affected sib-pair analysis, which strongly suggests that apoE4 influences HDL-C levels in children with FH. Moreover, the strong association suggests that apoE4 carries an additional disadvantage for children with FH.

In **chapter 4** we investigated the effect of the type of LDL receptor mutation on lipoprotein metabolism in children with FH. As a result of less environmental influences and late onset of additional lipid disorders, the effect is probably more accurately analyzed in children than in adults. In a large pediatric FH cohort, free from selection for CVD, we estimated the influence of different LDL receptor gene mutations on lipoprotein metabolism. In addition, we investigated whether or not the parental risk of CVD was related to the type of mutation.

A total of 75 different LDL receptor mutations were identified in 645 children with heterozygous FH. Null alleles were associated with significantly more elevated LDL-C levels compared with receptor-defective mutations. The parental CVD risk was not significantly different between carriers of null alleles and receptor-defective mutations. The specific N543H/2393del9 mutation resulted in a less atherogenic lipid profile with significantly less increased LDL-C and triglyceride levels and a tendency to higher HDL-C levels. Moreover, the parents with the N543H/2393del9 mutation had less often CVD relative to parents with other mutations.
Our findings suggest that some specific LDL receptor mutations may be expressed as mild FH and cause less CVD. However, the large variation of LDL-C levels between carriers of receptor-negative mutations and receptor-defective mutations does not seem to be clinically relevant. Moreover, so far unidentified, familial factors underlie the difference of lipoproteins that may contribute to the burden of the disorder.

In **chapter 5** the preconditions for validated surrogate markers of atherosclerosis, and why B-mode ultrasound intima-media thickness (IMT) measurements meet these requirements, are identified.

Atherosclerosis is a protracted disease process of the arterial wall with onset decades prior to its clinical manifestations. To understand the determinants of the process and develop therapeutic approaches requires a lifelong follow-up if clinical endpoint data are used. This approach needs extensive time and resources. Therefore validated surrogate markers for atherosclerosis that can efficiently identify and describe populations at cardiovascular risk and investigate therapeutic regimens have drawn

increasing attention. An ultrasound imaging and image analysis protocol is presented in this chapter to accentuate the need for standardization within and throughout studies if IMT measurements are used for modeling of arterial wall changes.

Because myocardial ischemia is often observed in early adulthood in patients with FH, a crucial remaining question regarding this disorder is whether lipid-lowering therapy should be restricted to adult patients or already initiated in childhood. In **chapter 6** we, therefore, assessed at what age morphological arterial wall changes can be observed in children with FH and determined which factors contribute to this process. First, a cross-sectional study of a large cohort of heterozygous children with FH and unaffected siblings was performed using B-mode ultrasound assessment of the carotid arterial wall. Second, independent predictors of carotid wall thickness were identified with multivariate regression analysis.

Mean carotid IMT in children with FH was significantly greater than in controls. These cross-sectional data suggest at least a 5-fold more rapid progression during childhood in children with FH versus their normolipidemic siblings. The different progression rates in children with FH led to a statistically significant IMT deviation from normal around the age of 12 years. Multivariate analysis revealed LDL-C, age, and gender as strong and independent predictors of IMT.

So, the structure of the arterial wall starts to deviate from normal in children with FH well before puberty. Age, gender, but most important, LDL-C levels contribute to this process.

Treatment with HMG-CoA reductase inhibitors (statins) in adults is very effective in coronary artery disease prevention, although the majority of events in FH cannot be avoided. Treatment with these compounds should therefore probably be started before adulthood. Pharmacokinetic data on these drugs in children are lacking, which makes it difficult to devise a rational dosing scheme for children. In **chapter 7** we carried out a two-week, multiple dose, pharmacokinetic study with pravastatin in 24 children with FH, aged 8 to 16 years. Half of these children were prepubertal. All children received 20 mg of pravastatin once daily and a plasma-concentration versus time curve was performed on day 14. Pharmacokinetic curves for each individual were constructed using non-parametric methods, yielding Area Under Curve (AUC), peak serum concentration (C_{max}), and apparent terminal half-life ($t_{½}$). Results showed that pravastatin was well tolerated. The C_{max} in prepubertal children differed non significantly from the C_{max} in adolescents, neither did AUC in prepubertal children differ significantly from AUC in adolescents. The $t_{½}$ was the same for both groups. A 27% LDL-C reduction from baseline was achieved at day 14. An inversed correlation was found between C_{max} and age. There was no relationship between any PK parameter

and cholesterol lowering. PK parameters and effect size were not different from previous studies in adults.
Based on our findings there are no reasons to treat children with FH between ages of 8 and 16 with dosage regimens that are different from those in adults. However, for prepubertal children half the advised starting dose for adults may be sufficient.

Atherosclerotic disease involves inflammatory and immunologic mechanisms, but the sequence of immunomodulatory steps and which molecule(s) having key roles early in atherogenesis is not clear. Micro C-reactive protein (μ-CRP) is established as an inflammatory marker of atherosclerosis. Neopterin, a marker of cellular immune activation, is produced by human macrophages. HMG-Co A reductase inhibitors, statins, have been recognized as immunomodulators and reduce cardiovascular events and mortality.

In the **addendum** we described the levels of neopterin and μ-CRP in children with heterozygous FH because FH has been regarded as a model of atherosclerosis. We evaluated the impact of pravastatin on children with FH and their unaffected siblings.

There were no differences between the groups concerning demographic data. The children with FH had a significant elevated level of neopterin compared to normal siblings. Furthermore, two years of pravastatin therapy reduced the neopterin level significantly. Concerning μ-CRP at baseline, there were no differences between the FH-children and siblings without FH, whilst μ-CRP continued to increase over two years in both FH-children receiving pravastatin and placebo. Our findings suggest that the cellular inflammatory marker neopterin is an early marker in the atherosclerotic process shown in this study in children with FH. This inflammatory response is modified by statins.

Children with FH have endothelial dysfunction and increased carotid IMT as heralds of the premature atherosclerotic disease they will suffer later in life. Although intervention in the causal pathway of this disorder has been available for over a decade in adults, the long-term efficacy and safety of cholesterol-lowering medication has not been evaluated in children. In **chapter 8** we describe a randomized, double-blind, placebo-controlled, two-year trial of daily treatment with pravastatin 20 - 40 mg in 214 children with FH, aged between 8 and 18 years. The primary efficacy outcome was defined as the change from baseline in mean carotid IMT over two years, whereas the principal safety outcome was measurement of growth, maturation and hormone levels over two years as well as changes of levels of muscle and liver enzymes.

Compared to baseline, carotid IMT showed a 10 micrometer regression on two year pravastatin, whereas a 5 micrometer progression was observed in the placebo

group. The change of IMT between the two groups differed significantly. No differences were observed for growth, endocrine function parameters, or pubertal development between the two groups.

In conclusion, two years treatment with pravastatin induces a significant regression of carotid atherosclerosis in FH children without adverse effects on growth, sexual maturation, hormone levels, liver or muscle tissue. The study demonstrates that treatment with pravastatin in children with heterozygous FH is efficacious and safe.