Childhood initiated statin therapy in familial hypercholesterolemia
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CHAPTER 14

SUMMARY
In addition to a general introduction, a summary and a general discussion, this thesis comprises eight original studies, a meta-analysis, two narrative reviews and a guideline proposal for the Netherlands, all on Familial Hypercholesterolemia and its treatment during childhood. Overall, the work presented seeks to answer the question whether childhood initiation of statin therapy in FH is effective and safe.

The general introduction, **chapter 1**, provides an historic overview of the link between high plasma levels of cholesterol and atherosclerotic cardiovascular disease, familial hypercholesterolemia, and statins. In **chapter 2**, we discuss the use of lipid-lowering drugs in children. Also, manifestations of Familial Hypercholesterolemia (FH) in childhood are considered. In **chapter 3**, we present a study addressing the molecular basis of autosomal dominant hypercholesterolemia (ADH). From a cohort of 1430 children referred to our Lipid Clinic, we selected 269 patients with a clinical FH phenotype and no other conditions predisposing for hypercholesterolemia. In these individuals, a functional mutation was identified in 95% of cases (95% in the gene encoding the low-density lipoprotein (LDL) receptor; 5% in the gene encoding apolipoprotein B). In contrast to what is claimed in previous reports, this indicates that most of the large-effect genes underlying ADH are known to date. In **chapter 4** we investigate the follow-up of children after a genetic diagnosis of FH has been established. We approached 322 parents of FH patients, 18 months after diagnosis. Two hundred thirty-three of them gave consent for participation and received a questionnaire covering topics such as demographics, family history, physician consultation, and treatment. Of 207 respondents aged 10.9±4.2 years (mean±standard deviation (SD)), 79% consulted a physician, of which only 37% was eventually treated by a lipid-clinic specialist. LDL-cholesterol (LDL-C) level at diagnosis and a positive family history for cardiovascular disease were independent predictors for physician consultation. Of those who consulted a physician, 62% reported to have received lifestyle advice, and 26% were prescribed statin treatment. This study shows that the follow-up of children, diagnosed by the Dutch screening program, is inadequate, due to absence of physician consultation or non-referral by consulted physicians. These results underline that implementation of adequate follow-up is a prerequisite for an effective FH screening program. **Chapter 5** comprises a systematic review and meta-analysis of 6 high quality randomized, double-blind placebo-controlled trials evaluating the efficacy and safety of statin treatment in a total of 798 children with FH. These studies were all carried out between 1996 and 2005. Treatment duration was 12 to 104 weeks. Lipid-lowering efficacy of the investigated statins was similar to that observed in adults. Furthermore, this meta-analysis did not reveal significant differences in safety outcomes such as sexual development, or muscle or liver toxicity. We found a minimal, clinically non-significant,
difference in growth in favor of the statin group (0.33 cm; 95% confidence interval 0.03 to 0.63 cm). These results support the notion that statin therapy in children is safe, although further studies are required to assess lifelong safety. In chapter 6 we present the results of the PLUTO study: a three month, double-blind, randomized, placebo-controlled trial, followed by a 10 months open-label, titration to-goal extension phase that sought to assess the efficacy and safety of rosuvastatin in children aged 10-17 years with FH. Despite an average LDL-C reduction of 50% in the group treated with the highest dose of rosuvastatin (20 mg), the LDL-C goal of 2.8 mmol/l was achieved in only 40% of the participants, reflecting high baseline LDL-C levels. As with the other statin-studies in children with FH, no safety issues were revealed in this trial. Chapter 7 reports a sub-study of the PLUTO study, in which we investigated the consequences of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibition by rosuvastatin for coenzyme Q10 (CoQ10) levels and mitochondrial adenosine triphosphate (ATP) synthesis. As for cholesterol synthesis, HMG-CoA reductase is the first committed and rate-limiting enzyme for CoQ10 production. CoQ10 plays a key role in mitochondrial respiratory chain driven ATP synthesis. Although CoQ10 levels in peripheral blood mononuclear cells from rosuvastatin treated subjects (n=29) significantly decreased from baseline (32%, p=0.02), ATP production in these cells was not affected (p=0.6). Whether changes in CoQ10 status play a role in clinical adverse events remains to be established. Chapter 8 addresses another drug efficacy and safety study, with a design similar to the PLUTO study. First, in an eight month randomized double-blind, placebo-controlled period, ezetimibe, a cholesterol absorption inhibitor, combined with simvastatin was compared to treatment with simvastatin and placebo. In the second phase of the study, all subjects (n=248) received simvastatin plus ezetimibe for 5 months. Coadministered ezetimibe 10 mg and simvastatin 40 mg led to a significantly greater reduction in LDL-C levels than treatment with simvastatin 40 mg alone (54% versus 38%, p<0.01). All treatment regimens were well tolerated throughout the study period of a little over a year. In chapter 9, the AfterTen study is described. In this study we assessed long-term efficacy and safety of childhood initiated statin therapy. All 214 FH patients who were included in a previous paediatric trial in our centre (and were prescribed statin therapy since), were eligible. Now, ten years later, we invited them for a study visit including physical examination, blood lipid- and safety parameters, and measurement of carotid intima-media thickness (c-IMT). Non-affected siblings, of whom we also had baseline measurements, were included as controls. Follow-up was successful in 90% of subjects (age 18-30 years). Measures of LDL-C and absolute c-IMT were significantly higher in FH subjects, but progression of c-IMT was similar to the level observed in controls. This is reassuring in terms of cardiovascular risk reduction. The age of statin initiation was a significant predictor for c-IMT, suggesting that earlier
treatment results in better prevention of atherosclerotic cardiovascular disease. Moreover, and probably most important, no untoward safety effects were observed. In chapter 10, we evaluated the tolerability and adherence of statin therapy by using validated questionnaires in the AfterTen cohort (n=214): young adult FH patients that initiated statin therapy in childhood, ten years before. Follow-up was successful in 95% of subjects (age 18 to 30 years). Side effects, experienced in the last ten years, were reported by 20% of the patients, mainly consisting of myopathy and gastrointestinal symptoms. Three patients (1.5%) discontinued statin therapy due to side effects. Rhabdomyolysis or other major adverse events were not reported. Of the 168 patients (82%) who remained on treatment, 79% took >80% of their pills in the last month. None of the patient characteristics was significantly associated with adherence. In chapter 11 a Dutch national treatment guideline proposal for children with FH, published in 2008, is presented. Under the age of 8, we recommend counselling of parents and children and lifestyle advice. Pharmacological treatment is recommended from 8 years of age onwards, when LDL-C is above 4 mmol/l, despite lifestyle advice. As opposed to the above-mentioned studies that deal with diagnosis and treatment of children with FH, the last chapters cover a different field. In chapter 12 we present a literature review of the consequences of hypercholesterolemia during pregnancy in FH patients, for both the pregnant woman and the unborn child. When pregnancy is considered, lipid-lowering drugs are often discontinued for fear of teratogenic effects. Human and animal studies suggest an enhanced tendency towards atherosclerosis in offspring of mothers who suffer from hypercholesterolemia during pregnancy. However, these studies need further confirmation due to limitations such as cohort size and clinical sampling bias. We sought to provide such confirmation in chapter 13. Here we present the results of a study comparing carotid intima-media thickness and lipid profiles of offspring from FH mothers and FH fathers, from 3 different cohorts (total n=3353). The outcomes do not support the hypothesis that offspring from FH mothers have an increased cardiovascular risk as compared to offspring from FH fathers. Chapter 14 comprises the overall summary. Finally, in chapter 15, we provide a general discussion of the results presented in this thesis. Together with previous research, the studies presented form a solid basis for childhood initiation of statin treatment in FH patients. Further research should focus on three aspects: life-long safety of statin therapy, the optimal age of treatment initiation, and optimal treatment goals in children with FH.