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Pediatric implications of heterozygous familial hypercholesterolemia

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Chapter 1

Introduction and
outline of this thesis

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Introduction

Familial hypercholesterolemia (FH) is an autosomal co-dominant inherited metabolic disorder that predisposes to early onset of atherosclerosis.¹ In the Netherlands, the estimated prevalence of heterozygous FH is 1:400.² The underlying defect is a mutated low-density lipoprotein (LDL) receptor, which results in elevated plasma LDL cholesterol levels.³ The disorder is molecularly heterogeneous: over 800 sequence variations in the LDL receptor gene have been described that can be divided into six functional classes.^{4,6} On physical examination, adult patients may have characteristic xanthomas on the Achilles' tendons and the extensor tendons of hands and feet. Children with heterozygous FH usually do not display these clinical signs, although they have increased plasma cholesterol levels from birth onwards. FH has virtually full penetrance. After diagnosis, adult FH patients are treated lifelong with β -hydroxy- β -methylglutaryl coenzyme A reductase inhibitors (statins).

Should we detect heterozygous FH in children?

Children with homozygous FH are not studied in the present thesis. Homozygotes are rare and they suffer from a much more severe disorder leading to juvenile onset of cardiovascular disease and premature death.¹ Moreover, they are often resistant to treatment with statins. Of course they need to be detected as soon as possible and aggressively treated thereafter.

The clinical sequelae of heterozygous FH are expressed during adulthood as an increased risk of cardiovascular disease that causes excess mortality.⁷⁻¹¹ Statin treatment of FH adults leads to a clear inhibition of the progression of the vascular damage.¹² Although statin treatment could be considered as intervention in the causal pathway of heterozygous FH, it does not completely restore the arterial wall. In line with this observation, the findings of a large follow-up study in the United Kingdom suggest that statin treatment of heterozygous FH adults does not normalize their cardiovascular disease risk.¹³ In prepubertal children with heterozygous FH, endothelial function is already impaired.¹⁴ In addition to early functional changes, accumulation of LDL cholesterol deteriorates the vascular morphology and this associates with an increased intima-media thickness (IMT) of the carotid arteries.¹⁵⁻¹⁷ In line with these observations, myocardial ischemia and coronary artery stenoses have been documented in young adults with this disorder.^{18,19} Hence, postponing statin treatment until adulthood might allow the development of significant arterial lesions in young FH patients. Accordingly, early initiation of statin treatment in children with FH might be advantageous, but unfortunately, studies of such treatment have only addressed short-term tolerability and safety.²⁰⁻²³ The significance of diagnosing heterozygous FH in children clearly depends on the severity of atherogenesis and the long-term safety of statins.

How should we detect FH in children?

Each child of a parent with heterozygous FH has 0.5 probability of inheriting the disorder. Among these parents, the diagnosis FH could be based on gender- and age-specific 95th percentiles of LDL (and total) cholesterol levels. However, a considerable number of false-negative and false-positive diagnoses might be expected as shown among adults in families with FH.²⁴ Moreover, variable expression of FH over time, as well as the frequent occurrence of hypercholesterolemia in our general population caused by other disorders could increase the number of false diagnoses in children. FH is a monogenic disorder with high penetrance. Nonetheless, large variation of the clinical consequences has been observed among carriers of LDL receptor mutations.^{25,26} Likely, unknown additional familial risk factors for cardiovascular disease determine the burden from the disorder.^{25,27,28} Identification of these additional risk factors could improve the detection of children with FH who are at particularly high risk of early atherosclerosis. Individual regimens may then be applied to prevent early onset of atherosclerosis in children with FH.

Outline of this thesis

In **chapter 2**, the clinical data are described of a very large cohort of children with FH. This chapter gives all the characteristics with regard to physical stigmata and lipoprotein abnormalities of childhood FH. Among the children, the risk factors and their relation with cardiovascular disease 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 future cardiovascular disease.

In **chapter 3**, the lipoprotein profile is further refined to the apolipoprotein E genotype. We analyzed the effect of the apolipoprotein E alleles on the lipoproteins in 450 unrelated children with FH and 154 affected sib-pairs.

The future risk of cardiovascular disease of a child with FH may be at least partly based on the nature of the particular LDL receptor mutation. **Chapter 4** reports the genetic heterogeneity at the LDL receptor locus in the large cohort of children with FH in relation to clinical parameters and the parental risk of cardiovascular disease.

In order to assess the atherosclerotic burden and preatherosclerotic arterial wall abnormalities in children with FH a non-invasive technique could be of great importance. The measurement of the arterial wall IMT of the carotid and femoral arteries by B-mode ultrasound has developed into such a technique. **Chapter 5** introduces this technique to children and provides data on standardization and validation of carotid IMT. In **chapter 6** we compared children with FH to their normolipidemic siblings. We assessed at what age morphological arterial wall changes in mean carotid IMT can be observed in children with FH and determined which factors contribute to this process.

However, the indication to diagnose FH and assess the risk of cardiovascular disease in children clearly depends on the availability of effective and safe treatment. In heterozygous FH, treatment with statins is an intervention in the causal pathway. Long-term use of this medication has only been studied in adults. Before we could study statin therapy in children with FH, we had to perform a pharmacokinetic study of pravastatin in this age category. **Chapter 7** reports this study. Thereafter, we set out to analyze the consequences of statin therapy in childhood FH on a large number of laboratory parameters and on carotid IMT. In an **addendum**, the effect is estimated of the pravastatin on inflammatory markers as neopterin and μ CRP. As final proof that statins decrease the atherosclerotic burden in children with FH, we studied the two-year efficacy of this drug towards carotid IMT. We describe the results of this randomized, double-blind, placebo-controlled trial in **chapter 8**.

The last part of the present thesis is a summary that describes almost a ten-year period of clinical research into childhood FH.

References

1. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed. New York, McGraw-Hill 2001; vol 3:2863-913
2. Lansberg PJ, Tuzgöl S, Ree MA vd, Defesche JC, Kastelein JJP. Higher prevalence of familial hypercholesterolemia than expected in adult patients of four family practices in Netherlands [in Dutch]. *Ned Tijdschr Geneeskd* 2000; 144:1437-41
3. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science* 1986; 232:34-47
4. Fouchier SW, Defesche JC, Umans-Eckenhausen MAW, Kastelein JJP. The molecular basis of familial hypercholesterolemia in The Netherlands. *Hum Genet* 2001; 109:602-15
5. Hobbs HH, Russell DW, Brown MS, Goldstein JL. The LDL receptor locus in familial hypercholesterolemia: Mutational analysis of a membrane protein. *Annu Rev Genet* 1990; 24:133-70
6. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. *Hum Mutat* 1992; 1:445-66
7. Jensen J, Blankenhorn DH, Kornerup V. Coronary disease in familial hypercholesterolemia. *Circulation* 1967; 36:77-82
8. Slack J. Risks of ischaemic heart disease in familial hyperlipoproteinaemic states. *Lancet* 1969; 2:1380-2
9. Heiberg A. The risk of atherosclerotic vascular disease in subjects with xanthomatosis. *Acta Med Scand* 1975(4); 198:249-61
10. Stone NJ, Levy RI, Frederickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. *Circulation* 1974; 49:476-88
11. Beaumont V, Jacotot B, Beaumont J-L. Ischaemic disease in men and women with familial hypercholesterolaemia and xanthomatosis: A comparative study of genetic and environmental factors in 274 heterozygous cases. *Atherosclerosis* 1976; 24:441-50
12. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001; 357:577-81

13. Scientific Steering Committee of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolemia: implications for clinical management. *Atherosclerosis* 1999; 142:105-12.
14. De Jongh S, Lilien MR, Bakker HD, Hutten BA, Kastelein JJP, Stroes ESG. Family history of cardiovascular events and endothelial dysfunction in children with familial hypercholesterolemia. *Atherosclerosis* 2002; 163:193-7.
15. Jarvisalo MJ, Jartti L, Nanto-Salonen K, Irjala K, Ronnema T, Hartiala JJ, Celermajer DS, Raitakari OT. Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. *Circulation* 2001; 104:2743-7.
16. Pauciuolo P, Iannuzzi A, Sartorio R, Irace C, Covetti G, Di Constanzo A, Rubba P. Increased intima-media thickness of the common carotid artery in hypercholesterolemic children. *Arterioscler Thromb* 1994; 14:1075-9.
17. Tonstad S, Joakimson O, Stensland-Bugge E, Leren TP, Ose L, Russell D, Bonnaa KH. Risk factors related to intima-media thickness and plaque in children with familial hypercholesterolemia and control subjects. *Arterioscler Thromb Vasc Biol* 1996; 16:984-91.
18. Mabuchi H, Koizumi J, Shimizu M, Takeda R, the Hokuriky FH-CHD Study Group. Development of coronary heart disease in familial hypercholesterolemia. *Circulation* 1989; 79:225-32.
19. Mouratidis B, Vaughan-Neil EF, Gilday DL, Ash JM, Cullen-Dean G, McIntyre S, MacMillan JH, Rose V. Detection of silent coronary artery disease in adolescents and young adults with familial hypercholesterolemia by single-photon emission computed tomography Thallium-201 scanning. *Am J Cardiol* 1992; 70:1109-12.
20. Knipscheer HC, Boelen CCA, Kastelein JJP, van Diermen DE, Groenemeijer BE, Van den Ende A, Buller HR, Bakker HD. Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. *Pediatr Res* 1996; 39:867-71.
21. Lambert M, Lupien PJ, Cagne C, Levy E, Blaiichman S, Langlois S, Hayden M, Rose V, Clarke JTR, Wolfe BMJ, Clarson C, Parsons H, Stephure DK, Potvin D, Lambert J. Treatment of familial hypercholesterolemia in children and adolescents: Effect of lovastatin. Canadian Lovastatin in Children Study Group. *Pediatrics* 1996; 97:619-28.
22. Stein EA, Illingworth DR, Kwiterovich PO Jr, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999; 281:137-44.
23. De Jongh S, Ose L, Szamosi T, Cagné C, Lambert M, Scott R, Perron P, Dobbelaere D, Saborio M, Tuohy MB, Stepanavage M, Sapre A, Gumbiner B, Mercuri M, van Trotsenburg ASP, Bakker HD, Kastelein JJP. Efficacy and safety of statin therapy in children with familial hypercholesterolemia. *Circulation* 2002; 106:2231-7.
24. Umans-Eckenhausen MAW, Defesche JC, Sijbrands EJG, Scheerder RLJM, Kastelein JJP. Review of first 5 years of screening for familial hypercholesterolaemia in The Netherlands. *Lancet* 2001; 357:165-8.
25. Sijbrands EJG, Westendorp RGJ, Paola, Lombardi M, Havekes LM, Frants RR, Kastelein JJ, Smelt AH. Additional risk factors influence excess mortality in heterozygous familial hypercholesterolaemia. *Atherosclerosis* 2000; 149:421-5.
26. Sijbrands EJG, Westendorp RGJ, Defesche JC, de Meier PH, Smelt AH, Kastelein JJ. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: Family tree mortality study. *BMJ* 2001; 322:1019-23.
27. Mastropaolo W, Matheny A Jr, Lang CA. Plasma cholesterol concentrations in twin children: Estimates of genetic and environmental influences. *Clin Chem* 2001; 47:771.
28. Leander K, Hallqvist J, Reuterwall C, Ahlbom A, de Faire U. Family history of coronary heart disease, a strong risk factor for myocardial infarction interacting with other cardiovascular risk factors: results from the Stockholm Heart Epidemiology Program (SHEP). *Epidemiology* 2001; 12:215-21.