Childhood initiated statin therapy in familial hypercholesterolemia
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CHAPTER 15

GENERAL DISCUSSION
The work presented in this thesis covers different aspects of statin treatment in children with familial hypercholesterolemia, ranging from mutation analysis, via studies on efficacy and safety of available therapies, to ‘real world’ clinical management. As announced in the introduction to this thesis, these studies seek to answer two essential questions concerning childhood initiated statin therapy in FH patients:

1) Is cholesterol-lowering therapy with statins in children with FH effective in terms of lowering blood cholesterol levels and coronary heart disease prevention?
2) Is cholesterol-lowering therapy with statins safe for children with FH?

In this final chapter I will discuss whether, and if so to what extent, these questions are indeed answered. Also, we propose directions for further research.

Efficacy in terms of lowering blood cholesterol levels
Undoubtedly, statins effectively lower total- and low-density lipoprotein cholesterol (LDL-C) levels in children with FH. Already a decade before the initiation of the studies collected in this thesis in 2006, the first two randomized-controlled trials that showed the lipid-lowering efficacy of lovastatin and pravastatin in children were published. Since then, all currently available statins have been proven effective and well tolerated in paediatric FH patients, except for pitavastatin which is currently investigated. In chapter 5, we present a systematic review and meta-analysis of 6 high quality double-blind randomized-controlled trials. A study investigating the efficacy and safety of rosuvastatin, the most potent statin studied in children thus far, is reported in chapter 6. Altogether, we conclude that reductions in serum lipids observed on statin therapy in children and adults are similar.

However, despite these significant reductions, LDL-C lowering in terms of current guideline achievement for paediatric FH patients (<3.3 mmol/l) is insufficient. This reflects the high baseline LDL-C levels in FH patients. In the titration-to-goal phase of the rosuvastatin trial with doses up to 20 mg in FH patients, presented in chapter 6, a third of the participants did not reach an LDL-C lower than 3.3 mmol/l, whereas the treatment goal set in the study of 2.8 mmol/l was not reached by 60% of patients. In another trial on improving lipid-lowering efficacy of therapy by adding the cholesterol absorption inhibitor ezetimibe to simvastatin, 77% had achieved LDL-C levels lower than 3.3 mmol/l and 63% attained the goal of 2.8 mmol/l. Thus, the search for novel, more potent therapeutic regimens in terms of lipid-lowering efficacy should be continued.

In the ‘real life clinical practice’ cohort of FH children reported in chapter 9 and 10, mean LDL-C was 4.4 mmol/l, despite good overall treatment adherence. LDL-C was 3.9
mmol/l in patients with excellent adherence. All these FH patients are now adults, with even stricter treatment goals (<2.5 mmol/l). Insufficient achievement of the treatment goals as advocated by guidelines has also been reported in studies on treatment efficacy in adult FH patients. For example, in Dutch patients with FH, the treatment goal of 2.5 mmol/l was reached in only 21% of patients. However, not all of these received maximal pharmacological treatment despite LDL-C levels above 2.5 mmol/l. Remarkably, the main reason for this was acceptance of a higher LDL-C target level by the treating physician. Apparently, besides insufficient efficacy of current treatment regimens, non-compliance or lack of knowledge with respect to existing guidelines by physicians (and probably also by patients as they are likely not aware of the guidelines) is an important reason for not reaching treatment goals.

**Efficacy in prevention of coronary heart disease**

The most important question addressed in this thesis, is whether cholesterol-lowering therapy with statins in children with FH is effective in the prevention of coronary heart disease later in life. The question would be best answered by a trial in which a large cohort of FH children would be randomized to statin initiation in childhood or young adulthood. Subsequently, participants should be followed for life, in order to assess the number of cardiovascular events. However, apart from the feasibility of such a trial, it is probably unethical to perform such a trial considering the accumulating, albeit indirect, evidence that childhood initiation of statin therapy is beneficial, at least in lowering LDL-C levels. For adult FH patients, a randomized controlled trial proving the efficacy of statin therapy in terms of cardiovascular event prevention has never been carried out because of these ethical considerations. Nonetheless, the benefit of statin therapy in preventing cardiovascular disease in non-FH adults is supported by robust evidence. Furthermore the benefit of statin treatment in adults with FH has been shown in retrospective studies, as discussed in chapter 9. In the prospective cohort study reported in this chapter, we show that in a cohort of children in whom statins were initiated during childhood, enhanced atherosclerosis was halted. The degree of carotid intima media thickness (c-IMT) progression, a well-validated predictor of future cardiovascular events, was similar in treated FH patients and non-FH controls. This study strongly supports the notion that childhood initiation of statin therapy indeed prevents progression of the processes leading to atherosclerosis and consequently the incidence of cardiovascular events and related deaths later in life.

The notion that early initiation of statin therapy in children with FH is beneficial in terms of prevention of cardiovascular disease sparks a need for early diagnosis and follow-up in these patients. Several countries set up screening programs in order to identify FH
patients; some based on phenotype, others on genotype. Genetic screening programs require sufficient mutation detection rates in patients with the clinical FH phenotype. In chapter 3, we show that, when rigorous criteria are used to select patients with the FH phenotype in a pediatric cohort, and when thorough molecular diagnostic methods are applied, a mutation can be identified in 95% of cases. This implies that most of the large-effect genes underlying FH have been discovered, which contributes to the feasibility of genetic screening. Nonetheless future genetic studies should seek for the molecular basis underlying FH of those few patients in whom no mutation can yet be found.

Adequate diagnosis is worthless without subsequent follow-up and treatment according to set guidelines. In chapter 4 we show that even after an unequivocal diagnosis of FH, followed by an explicit written recommendation to visit a physician for further follow-up, over 20% does not do so. Therefore, adequate follow-up as an integrated part of diagnostic programs for FH patients should be pursued.

Once diagnosed and under medical care, attention needs to be paid to compliance to the prescribed treatment. In chapter 10 we report that in our cohort of FH patients who started statin therapy in childhood, adherence and tolerability after 10 years of follow-up were remarkably good. It may be that early initiation of therapy contributes to habitual use of medication as a part of ‘normal life’.

**Are statins safe in children with Familial Hypercholesterolemia?**

This is the second question asked in the introduction of this thesis. Given the effect of statins on endogenous cholesterol biosynthesis, concerns have been raised about the use of these drugs in children. Cholesterol plays a pivotal role in human physiology, for example as a constituent of cell membranes and a variety of hormones. Children with inborn errors of cholesterol synthesis, leading to very low levels of cholesterol, have severe clinical disease. However, as reviewed in chapter 2, several pediatric studies (in both FH and non-FH subjects) reveal an excellent safety profile, although all of these studies are of limited size and duration. By performing a meta-analysis presented in chapter 5 we sought to strengthen the evidence on the safety of statins in children. In addition, safety outcomes were evaluated in all statin trials presented in this thesis (chapter 6, 7 and 8). In the prospective cohort study presented in chapter 9 we assessed safety parameters of almost 200 children with more than 10 years of follow-up. No adverse safety effects were found, with all subjects being followed into adulthood. Furthermore, the safety of statins in adults is firmly established. Thus far, all evidence acquired supported the safety of statin use during childhood. However, available studies are statistically underpowered for the detection of more rare or subtle outcomes with
a large natural variation. Obviously, further safety data should be gathered from larger cohorts with longer follow-up in the future.

Related to the issue of safety of long-term statin treatment, is the question whether statin therapy should be continued in females during pregnancy. Current guidelines recommend discontinuation because of a supposed risk for teratogenic effects, which may lead to severely elevated LDL-C levels in pregnant FH patients. In chapter 12 we review current literature about the consequences of profound hypercholesterolemia during pregnancy in women with FH, and discuss the hypothesis that in utero exposure to high cholesterol levels may contribute to cardiovascular disease (long) after birth. This hypothesis is tested, but not supported in chapter 13.

In conclusion, knowledge of safety and efficacy must be weighed in order to constitute rational treatment guidelines. Chapter 11 comprises such a guideline for Dutch paediatricians published in 2008, which is largely in line with current international guidelines with respect to treatment of FH. The studies presented in this thesis support these guidelines.