Childhood initiated statin therapy in familial hypercholesterolemia
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CHAPTER 1

GENERAL INTRODUCTION

Hans J. Avis
“Today, we know that we are winning the war against coronary heart disease.”

This statement was made by lipid-icon Daniel Steinberg in 2004.\(^1\) Whether it holds true or not, with coronary heart disease still being the world leading cause of mortality\(^2\), there are still many battles to be fought. This thesis is focussed on a particular battlefield in this war: prevention of coronary heart disease in patients with familial hypercholesterolemia (FH). FH is the most common autosomal dominant inherited metabolic disorder. Before, it was estimated to affect approximately 1 in 500 individuals\(^3\), but recent studies report a much higher prevalence\(^4\). Severely elevated cholesterol levels that dramatically increase the risk for coronary heart disease characterize FH.\(^5\) More specifically, this thesis focuses on FH patients in the period of their life that most probably allows the best opportunity for preventive measures: childhood. It presents a sequel to more than a decade of research on this topic performed by my predecessors and supervisors, whose work will often be referred to throughout this thesis. In the battle against coronary heart disease in FH patients, this thesis seeks to contribute to the answers to the following two questions:

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?

As a general introduction to my theses, and to put the research presented in a broader perspective, I will briefly touch upon the history of its major ‘ingredients’: the link between cholesterol and coronary heart disease, FH, and statins. Previous achievements in the specific field of drug treatment in children with FH are reviewed in the next chapter. A brief overview of the work presented in this thesis is provided in chapter 14 (summary).

**Cholesterol and atherosclerotic coronary heart disease**

A little over a century ago, a young Russian pathologist at the Military Medical Academy in St. Petersburg named Nikolai N. Anitschkow, noticed that atherosclerotic coronary heart disease was an illness especially affecting wealthy men. Atherosclerosis was already known to accompany the process of ageing, but the pathogenesis of its progression was entirely unknown. Anitschkow presumed that the cholesterol rich diet of organ meat of these wealthy men might have played a role in their atherosclerotic coronary heart disease development. In 1913, he tested his hypothesis in a rabbit model. He observed that cholesterol fed rabbits developed vascular lesions similar to human atherosclerotic
plaques, whereas rabbits on a low-cholesterol diet did not show these lesions. In fact, he noticed that the amount and extent of the lesions was proportional to blood cholesterol levels. Anitschkow speculated that the lesions resulted from cholesterol that infiltrated the arterial wall from the blood. Furthermore, he suspected the cholesterol-loaded cells visible in the atherosclerotic lesions to be white blood cells.

The key roles of cholesterol and the immune system in the pathogenesis of atherosclerosis are now widely accepted by both professionals and laymen. However, for decades even well respected scientists have considered Anitschkow’s experiments non-relevant to human atherosclerosis. This was partly due to the fact that his findings could not be reproduced in other animals, such as dogs. Later, it turned out that these animals were mostly carnivores with an extremely efficient cholesterol and bile acid metabolism. Therefore, their blood cholesterol did not rise to levels high enough to enhance atherosclerosis, when their cholesterol intake was increased. Nonetheless eventually, a plethora of experimental, epidemiologic, genetic, and intervention studies have gradually replaced the scepticism concerning the link between hypercholesterolemia and atherosclerotic coronary heart disease. The Seven Countries Study, published in 1966, showed that dietary cholesterol intake, blood cholesterol levels, and the incidence of coronary heart disease were almost linearly correlated across seven different countries, with the Japanese showing the lowest cholesterol intake and blood cholesterol levels and the lowest incidence of coronary heart disease. The subsequent Japanese Migration Studies showed that Japanese individuals who moved to the United States of America, with a diet richer in cholesterol, had higher blood cholesterol levels and more heart attacks than their relatives in Japan. This indicated that the difference in the incidence of coronary heart disease was attributable to environmental factors (most likely dietary saturated fatty acids) instead of differences in genetic make-up. Data from the famous Framingham Heart Study cohort, being followed since 1950, further established the link between blood cholesterol (and many other risk factors such as blood pressure, smoking, and diabetes) and coronary heart disease. The final answer to the question whether cholesterol is correlated with coronary heart disease was delivered by numerous (randomized, double-blind) intervention studies, showing that cholesterol lowering by both diet and drugs lowers the incidence of cardiovascular disease.

While the epidemiologic evidence was accumulating, scientists with a more biochemical approach identified the blood lipoproteins and their metabolism. Low-density lipoprotein cholesterol (LDL-C) was shown to be the most pro-atherogenic lipoprotein. In contrast, high-density lipoprotein cholesterol appeared to be associated with a lower risk for coronary heart disease. In the sixties of the previous century, Donald S. Fredrickson
started to classify the lipoprotein patterns of his patients into separate categories. Although nowadays mostly replaced by nomenclature based on the molecular basis of disease, the Fredrickson classification has until recently served the diagnosis and treatment of dyslipidaemias.13

More than a century of research has unmasked the process of atherosclerosis as a complex interaction between the arterial wall, lipoproteins and the immune system.14 This process is present from birth onwards15, and commences with altered homeostatic properties and dysfunction of the arterial wall (endothelial injury), that may be induced by factors such as elevated LDL-C, free radicals caused by cigarette smoking, hypertension, diabetes and infectious microorganisms. Leukocytes bind to adhesion molecules expressed on the injured endothelium, to penetrate the vascular wall and become tissue macrophages. These macrophages subsequently instigate the inflammatory response that characterizes atherosclerosis. Atherogenic lipoproteins, such as LDL-C, are absorbed by the macrophages after they have been oxidized, thereby transforming these cells into foam cells. After apoptosis, these foam cells empty their contents into the inflamed vascular wall. T-cell infiltration into the vascular wall enhances the inflammatory process, as well as inducing smooth muscle cell proliferation. A further cascade of processes leads to the formation of an atherosclerotic plaque that is characterized by fibrosis, extracellular matrix proteins and atheroma. Due to the continuing process of inflammation, such a plaque might rupture and its contents might be exposed to the arterial lumen, leading to acute occlusion, as occurs in myocardial infarction and ischemic stroke.14

Familial hypercholesterolemia
Interestingly, and even closer related to this thesis than the above-mentioned, case-reports about children presenting with xanthomas (deposits of lipids beneath the skin, or attached to tendon sheets) and coronary heart disease at young age, had been published decades before the work of Nikolai Anitschkow. In 1939, the Norwegian internist Karl Müller reviewed such cases, and described a familial syndrome of xanthomas, hypercholesterolemia and angina pectoris as a “well defined clinical entity”, later named FH. He was convinced that xanthematous deposits in the coronary arteries and consecutive myocardial ischemia caused angina pectoris. FH later became apparent as one of the most common monogenetic autosomal dominant inherited genetic defects.6

In 1985 Michael S. Brown and Joseph L. Goldstein received the Nobel Prize for their identification of the LDL-receptor as the pivotal protein in regulating blood LDL-C levels, and its encoding gene as defective in FH. Their discovery was a breakthrough for
medicine and receptor biology in general. More than a decade before, they had wrongly but fruitfully proposed that cellular cholesterol overproduction caused FH. Thus, they investigated the rate of cholesterol synthesis in human fibroblasts, by studying hydroxy methylgluarcy (HMG)-coenzyme A (CoA) reductase. HMG-CoA reductase was earlier revealed to be the rate-limiting enzyme in cholesterol synthesis. This was another discovery awarded with a Nobel Prize, to Konrad Bloch, in 1964. Brown and Goldstein first showed that in normal cells, cholesterol synthesis increased when these cells were grown in a medium that lacked LDL-C, whereas it was suppressed in an LDL-C rich medium. However, in cells from FH patients this suppression was absent. Thus, Brown and Goldstein adapted their hypothesis and concluded that the cause of FH must be a defect in some "hitherto unidentified gene whose product is necessary for mediation of feedback control by lipoproteins". In further experiments, they discovered that the FH cells did suppress cholesterol synthesis when pure cholesterol dissolved in alcohol was added to the medium. The FH cells were thus able to respond as normal, provided the cholesterol got into the cells, but were unable to take up cholesterol as a component of LDL. Brown and Golstein subsequently characterized the LDL-receptor and its production from gene transcription to functional protein.13,16

Nowadays, more than a 1000 functional mutations in the LDL-receptor gene are known to underlie FH.17 In addition, mutations in the gene encoding apolipoprotein B-100, the carrier protein of cholesterol in the LDL-particle, are identified as another cause of FH, since the mutated apolipoprotein B-100 can not efficiently be taken up by the LDL-receptor.18 Rarely, gain-of-function mutations in proprotein convertase subtilisin/kexin 9 (PCSK9), a protein that promotes LDL-receptor degradation, cause FH.19 Nonetheless, not all cases of the FH phenotype can be explained by genetic defects yet.20

Clinically, FH is characterized by LDL-C levels elevated about tenfold in homozygous patients, and threefold in patients heterozygous for FH. Depositions of cholesterol in tissues may be visible as tendon xanthomas, xanthelasmata or arcus cornealis.21 If untreated, heterozygous patients develop coronary artery disease before the age of 60 in 85% of males and 60% of females.22 No randomized placebo-controlled trials have been carried out to investigate the effect of LDL-C lowering treatment on the incidence of cardiovascular events in subjects with FH specifically. Nonetheless, considering the evidence on the efficacy of treatment of hypercholesterolemia in non FH-subjects12 and the fact that several studies have strongly supported the benefit of pharmacological treatment in FH patients21,22, it would be unethical to ever do so. Early initiation of statin therapy is currently the mainstay of FH treatment.23,24 However, both the optimal age of treatment initiation, and optimal therapeutic goals remain unknown. Furthermore, there
are safety concerns about childhood initiated life-long statin therapy, although scientific data have thus far not justified these concerns. As mentioned before, these issues are at the centre of this thesis. Due to the fact that early primary prevention requires early and unequivocal diagnosis, genetic screening programmes for FH are active in several countries, including the Netherlands.

**Statins**

While Brown and Goldstein were heading towards the discovery of the LDL-receptor, Akira Endo on the other side of the world in Tokyo, was about to make a breakthrough discovery regarding safe and effective drug therapy to lower blood cholesterol. The existing bile-acid binding resins were poorly tolerated and of limited efficacy, and the search for safe drugs that suppress cholesterol synthesis had been fruitless for decades. Akira Endo investigated fungi for antibiotic properties, but for some reason felt that his fungal species might produce natural cholesterol inhibitors. After testing over 6000 of them, he found one that did so. The isolated specific enzyme turned out to selectively inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. Endo and his co-workers pursued in developing this compound called compactin, that in 1980 proved able to lower human blood cholesterol levels by about 30%, but there were serious safety issues. The efficacy of compactin in lowering blood cholesterol of patients with FH was published the next year. Pharmaceutical companies started their search for better HMG-CoA reductase inhibitors, now known as statins. Various compounds, of increasing cholesterol-lowering efficacy, rode the long and rocky road from bench to bedside. Statins are considered the most effective drugs in lowering LDL-C levels, and are the most commonly prescribed drugs in the world. A large meta-analysis of statin trials shows that the incidence of major cardiovascular events is reduced by about 20% for each mmol/l decrease in LDL-C. The lower, the better, is the opinion of many clinicians when it comes to LDL-C goals in patients on statin therapy. Due to its efficacy in terms of coronary heart disease prevention, lipid-lowering therapy with statins is considered beneficial in an increasing number of medical conditions. To use another quote of Daniel Steinberg: *Some have proposed, only half in jest, that we put them (statins) in the drinking water.... it is noteworthy that in this new statin era, such proposals are no longer unthinkable*.
REFERENCES

17. www.ucl.ac.uk/fh, last visited April 2013.

