



Treat To Target Familial Hypercholesterolemia

-A prospective study on effects from maximal high intensive treatment of FH patients during eight years

Master Thesis by

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May 2015

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Summary

Background and aims: During the last decades there has been a formidable reduction in the mortality from cardiovascular diseases (CVD) in the western world, despite of this, CVD remains the leading cause of death. The underlying factor of nearly all CVD events is atherosclerosis. Familial Hypercholesterolemia (FH) is characterized by elevations of LDL cholesterol, and a 20-fold higher lifetime risk of early CVD when compared to the general population. Although FH is a relatively rare disease, it is of profound medical interest by serving as a model disease for atherosclerosis. Many FH patients will not reach the LDL treatment target even on high intensity medical treatment, hence modifiable risk factors becomes of extra importance. The aim of this study is to describe the effect of a maximally aggressive lipid lowering treatment and lifestyle intervention in a real life setting, monitored over eight years.

Subjects and method: In 2006 357 adult FH patients were recruited at the Lipid clinic during the routine consultations for visit 1 (V1) in the TTTFH-study. Data were collected through an ordinary medical examination, by the patients' records, and by three questionnaires and schemes dealing with medical data, lifestyle, opinions concerning the treatment. Visit 2 (V2) was conducted by the same protocol median one year after V1 with 332 patients who further participated. During the fall of 2014, visit 3 (V3) was carried out with a smaller group of 64 patients from the V2 population. We have compared the data collected at all three visits to examine the development for the group over time. Further we compared the patients who have developed CVD to those who have not, to describe what characterizes these patients.

Results: All blood parameters have improved over these eight years with the exception of triglycerides, fasting glucose and HbA1c. The number of patients who reached their LDL treatment target was significantly increased. Lifestyle variables, BMI, weight and waist circumference have all stayed constant or improved with increasing age. These FH patients were largely treated with high intensity statin therapy, where a considerable fraction also received dual or triple lipid medication. Side effects might be a problem for as many as 24 (37.5 %) patients. The comorbidities hypertension and diabetes was affecting 22 (34.4 %) and 6 (9.4 %) respectively. Low cholesterol has always been important to the patients, but on V3 there was a significant increase in how important the absence of side effects was considered to be. Comparing the CVD group against the non-CVD group, we found a significant difference

in the risk factors age, male gender, years of smoking, waist circumference, hypertension and diabetes, as well as in fasting glucose and HbA1c. They were also experiencing more side effects than the non-CVD group.

Conclusion: Under a maximally favorable condition customized to each single patient through the treatment at the Lipid clinic, the patients have improved or maintained nearly all of the variables they are measured by; many of these in contrast to the general population, and hence most likely have decreased their CVD risk considerably. Still, as the larger part does not reach the treatment target due to either considerable side effects or that they already receive full doses but have a lack of adequate responsiveness to the medication, and the search for other alternatives is of essence. When further looking into what characterized the individuals that develop CVD in our study population, we find a connection between classical risk factors and the occurrence of CVD. Those who lead a healthier lifestyle have less comorbidity and both respond better to medication and have lower severity of side effects.

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Abbreviations

APO A1	Apolipoprotein A1
APO B	Apolipoprotein B
BMI	Body mass index
CABG	Coronary artery bypass graft
95 % CI	95 % confidence interval
CIMT	Carotid intima-media thickness
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
ECM	Extra cellular matrix
FH	Familial hypercholesterolemia
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
IDL	Intermediate density lipoprotein
IL-18	Interlukin 18
IMT	Intima-media thickness
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol

LDLR	Low density lipoprotein receptor
LDLRAP1	Low Density Lipoprotein receptor adaptor protein
Lp(a)	Lipoprotein(a)
mCRP	Micro C reactive protein
MI	Myocardial infarction
Non-HDL	Non-High density lipoprotein
OUS	Oslo Universitets Sykehus (Oslo University Hospital)
PAR	Population's attributable risk
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/Kexin 9
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischaemic attack
UiO	Universitetet i Oslo (The University of Oslo)
V1	Clinical visit 1 at the Lipid clinic during the spring 2006
V2	Clinical visit 2 at the Lipid clinic during 2007
V3	Clinical visit 3 at the Lipid clinic during the second half of 2014
VLDL	Very low density lipoprotein

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1 Introduction

1.1 Cardiovascular disease

Cardiovascular diseases (CVD) are the collective term for atherosclerotic disorders of the heart and the blood vessels. Out of the 17,3 million deaths caused by CVD globally in 2008, coronary heart disease and stroke were the largest two subgroups, accounting for an estimated 13,5 million deaths worldwide, with CHD constituting the bigger part (1, 2).

During the last 40 to 50 years, there has been a formidable reduction in the mortality from cardiovascular disease in the western world and in Norway. It is assumed that 50 % of the reduction is due to an improvement in risk factors such as cholesterol, hypertension and blood sugar, as well as in lifestyle factors like smoking, unhealthy diet, and physical inactivity (3). Another 50 % of reduction is considered to be caused by the improvement of the primary and secondary medical treatments (4, 5). Nevertheless, despite these substantial advances in diagnostics and treatment, CVD still constitute approximately 30 % of all deaths, which leaves it the leading cause of death both in Norway, as well as in a global perspective (1, 6).

Recent trends in the developments in CVD have often been observed in younger age groups first. In Norway today 25-44 year olds is not seeing the same decrease in the number of heart attack admissions compared to the older age groups (6). This is in line with the World Health Organization projection of CVD to remain as the future leading cause of death (1). An increase in overweight, obesity and physical inactivity are thought to be important reasons for this (7).

Even though Norway sees a high number of CVD deaths, the prevalence of CVD is exceedingly higher, and many people experience non-lethal events, which might have a large impact on their quality of life.

1.2 Atherosclerosis

The underlying factor of nearly all CVD events is atherosclerosis. Atherosclerosis is a chronic inflammatory state in the vessel wall, caused by a complex interplay between lipoproteins, the immune system and the normal elements of the arterial wall(8). This process is initiated when circulating low density lipoprotein (LDL) particles penetrate into the vessel wall and are retained by anionic glycoproteins in the extracellular matrix (ECM), creating so called fatty streaks. Here, or already in the circulation, the LDL particle can be harmed through chemical modification such as oxidation or glycation, as it is isolated from the anti-oxidants in the plasma (9). These chemically modified particles are recognized by the scavenger receptors of macrophages, and are consequently phagocytised. There is a balance between the level of LDL cholesterol in the bloodstream and the level of LDL cholesterol penetrating the vessel wall, thus a high concentration of LDL cholesterol in the blood results in a potentially higher amount of chemically modified LDL cholesterol in the vessel wall. This higher amount of particles drives the macrophages to continue to engulf LDL cholesterol because of the lack of feedback regulation of the scavenger receptor, thus growing into cholesterol rich foam cells that accumulate at site, and often becoming necrotic. The foam cells secrete pro-inflammatory cytokines, initiating the inflammatory process. The cytokines recruit more macrophages that in turn become foam cells, and this characterizes an early stage. Soon, Type 1 T helper cells of the adaptive immune system enter and stimulate smooth muscle cells to proliferate and produce proteases that alter the ECM to be able to migrate (8). This eventually forms scar tissue and also transforms the lipid rich plaque to a fibrous and potentially calcified plaque, and creating stenosis. Since the inflammatory process continues, IL-18 among other cytokines, further drives the process, starting neovascularisation, and potentially eventually producing a thrombin. The vessel wall becomes thicker during this formation of the plaque, narrowing the artery cavity, and leading to reduced blood circulation to the organs, the heart, the brain and the peripheral arteries (10). The weakened wall may rupture creating a potentially harmful bleeding . It looks as though it's not the size of the plaque that determines the fate, but rather whether it is stable or unstable. A stable plaque is characterized by being capsulated. But when the plaque is accompanied by a high degree of inflammation, this will gradually break the capsule down. Often, a blood clot would cut off the blood supply to the tissue associated to the artery, giving rise to severe organ damage. If the organ in question is the heart, this might cause a MI, or if the site is the brain, the consequence would be a stroke (9, 11).

This atherosclerotic process is severely aggravated among the patients suffering from familial hypercholesterolemia (FH) (12). FH is the most prevalent dominant monogenetic disease, and its main feature is an inherited extreme elevated LDL-cholesterol.

1.3 Familial Hypercholesterolemia

Familial Hypercholesterolemia (FH), also called Müller-Harbitz' disease after the Norwegian doctors Carl A. Müller and Francis G. Harbitz, is characterized by elevations of serum LDL cholesterol, and a 20-fold higher lifetime risk of early coronary heart disease when compared to the general population (13).

1.3.1 Genetics and prevalence

FH is an autosomal dominant inherited disease that affects the clearance of LDL cholesterol from the circulation. Normally, the plasma membrane-bound LDL receptor (LDLR) especially highly expressed in the liver, binds circulating LDL cholesterol with apo B as a ligand. This initiates an endocytation of the LDL:LDLR complex through interactions involving the LDL receptor adaptor protein (LDLRAP1). Inside the cell the endosome matures and the LDL:LDLR binding is reversed due to the low pH, leaving the LDLR to be recycled back to the cell surface a process known as the receptor recycling. The late endosome further fuses with lysosomes, leading to a degradation of the LDL particle, and a release of the cholesteryl esters. This is one of several regulation points of the cell's LDLR level. If the LDLR is bound by proprotein convertase subtilisin/Kexin 9 (PCSK9), it is instead retained in the endosome and degraded in the lysosomes.

Among the patients suffering from FH this process is most commonly affected (> 90%) through a loss-of-function mutation in the LDLR gene, although there are also other mutations known to cause the same clinical FH phenotype. These are a loss-of-function mutation in the apo B gene, where the protein product becomes unable to bind the LDLR; a gain-of-function missense mutation in the PCSK9-gene resulting in an enhanced degradation of the LDLR; a loss-of-function mutation in the LDLRAP1gene that renders the endocytation process of the LDL:LDLR complex (14). For LDLR alone there have been identified more than 1600 mutation sites (15). These have been categorized based on whether the functional defects renders ligand binding, transport, internalization, recycling or is a null mutation. A

result from this genetic diversity is a variation in the severity of dysfunction, and hence a difference in the level of circulating LDL-C (14).

The European Atherosclerosis Society has ascertained that FH is a frequently undiagnosed disease. In Norway 1:300 is assumed to have heterozygous FH (HeFH), although recent Dutch estimates have suggested an even higher prevalence of 1:200 (16-19)(16-19)(16-19). In Norway this indicates that with 6400 genotyped FH patients today, there are still many undiagnosed patients. The prevalence of homozygous FH (HoFH) is very rare, traditionally estimated to affect only 1:1000 000. There are now 11 known patients with HoFH in Norway. With a population of approximately 5 million and an expected incidence of 1:10000000 only 5 HoFH should theoretically have been expected, indicating a higher prevalence of the FH genes. More than 50 HoFH have been diagnosed in the Netherland in contrast to the 20 expected also suggesting that FH is more frequent than previously believed (19).

1.3.2 Clinical presentation and features

Untreated FH may entail early heart disease and death. During earlier times 50 % of all men with HeFH had developed CVD in the form of MI or coronary death at a median age of 50 years. For women the corresponding median were 59 years of age (20). At an untreated TC in the area of 8 to 11 mmol/L, which was relatively normal for a HeFH patient during 1950 to around 1990, the risk of death from MI before the age of 50 was substantial for both sexes (13). The Simon-Broom Registry estimated an 125-fold increased CVD mortality SMR for untreated women and 50-fold for untreated men aged 20-39 years (21). HoFH patients have untreated TC values in the area of 12 to 30 mmol/L and, untreated could develop early-onset cardiovascular death already before the age of early teens. In HoFH the aggravated atherosclerosis start after few years of age, resulting for instance in visible xanthomas before the age of 3-4 years, related to the extreme levels of circulating LDL cholesterol particles (13).

It is also documented an early start of atherosclerosis in HeFH children, but fortunately to a much lesser degree related to the modest LDL cholesterol elevation compared to the HoFH children. Comparison of the carotid intima-media thickness (CIMT) between affected HeFH children with their non-affected siblings, have shown increased CIMT from the age of 10 and onwards (22). This is indicating that if you have a longstanding elevated LDL-cholesterol of

any cause, this will aggravate the progression of atherosclerotic disease, even already from the early age in childhood.

Physical signs of FH can be manifested for a HeFH patient during the late twenties due to lipid depositions in the tendons, in the iris of the eyes, and on eye lids, referred to as xantomata, arcus cornealis and xanthelasma respectively (figure x). They are a result of LDL-c depositions, and xantomata is the most characteristic of these for FH (13).

The xantomata is often seen as thickening of the Achilles tendons and sometimes in the extensor tendons to the fingers, but rarely elsewhere in the body. These are characteristic LDL-c depositions that will lead to inflammation and pain, and the level of Achilles tendons thickness is associated with an increased risk of CVD (23). Arcus cornealis is seen as a white line in the outer part of the cornea, and xanthelasma are flat yellow plaques in the eyelids, but are a nonspecific trait of FH, as it may also be present in individuals with polygenic hypercholesterolemia, and sometimes even with near normal cholesterol values.

1.3.3 Risk factors and treatment

Although FH is a relatively rare disease, it is of profound medical interest by serving as a model disease for atherosclerosis. The knowledge derived from FH is thus relevant for the rest of the population. All the other known risk factors for cardiovascular disease will further aggravate the atherosclerosis among FH patients.

The INTERHEART study found that 9 modifiable risk factors accounted for more than 90 % of the population's attributable risk (PAR) of developing the first myocardial infarction (MI) (24). Six of these factors were malicious, and three were protective against MI. When ranked from the highest percent of PAR, these risk factors are raised plasma lipids measured by the apoB/apoA1-ratio, active smoking versus never, combined psychological stressors, abdominal obesity and self-reported history of diabetes mellitus (DM) and hypertension. The protective factors in ranked order were daily intake of fruit and vegetables, regular physical activity and moderate alcohol intake. The latter was although a non-significant finding. These risk factors have since been confirmed by several other studies and summaries (Redegjøre for INTERSTROKE?, Burden of disease?), and are consistent across genders, different geographic regions and ethnic groups. WHO also estimates as much as 8 out of 10 MI events can be prevented through improvement in the diet and physical activity and quitting the

smoking (si noe om de to (stroke og MI) fra åkesson også? →indicating together with INTERSTROKE that nearly all premature MI's are preventable). There appears to be a synergistic effect when more than one risk factor is present, as the risk increases more than the sum would dictate. FH patients are as earlier described already at early increased risk through their high LDL cholesterol levels.

Raised plasma lipids

ApoB/apoA1-ratio (apo-ratio) was in the INTERHEART study found to account for 50 % of the PAR, and together with smoking it showed a graded relationship with the odds of a MI. Apo B is the major apolipoprotein of the atherogenic fraction of lipoproteins, hence a high apo B is associated with an increased risk of development of atherosclerosis and CHD.

Apo A1 is the major apolipoprotein on high density lipoprotein (HDL) particles. HDL is known for its crucial protective role in CVD through reverse cholesterol transport to the liver; removing lipids and cholesterol from the blood. It also exerts a further protective function by inhibiting aggregation and oxidation of LDL (25). A low HDL allows less protection and reverse transport, hence the amount of circulating lipids and cholesterol will be higher.

As the two apolipoproteins reflects opposite effects on the atherogenic risk and that there is only one apo B on each very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and LDL as well as one apo A1 on each HDL, the ratio reflects the balance between these fractions. This was found to be a better predictor of the CHD risk than any of the other traditional cholesterol values. However, in a follow up to one of these studies, apo-ratio was found to be equally predictive as LDL-c on CVD risk (26, 27).

Results from in vitro and animal studies, epidemiology (28-30), clinical trials (31, 32) and inherited forms of elevated LDL, like FH, indicate a strong causal relationship between LDL and CVD, and it is considered the most important risk factor for CVD. LDL accumulation is one of the first events in the development of atherosclerosis. A reduction in LDL level has been found to gain a 20 % lowering of mortality from CV events for each 1 mmol/L reduction in LDL cholesterol, and a 12 % lowering in mortality from all causes (27). However, by maintaining the lower cholesterol for a longer period of time than the duration of a clinical trial, the risk might actually be reduced even more than this prediction (32-34).

Over the years it has been discussed back and forth if triglycerides (TG) are an independent risk factor of CVD. Due to its interconnection with several other risk factors, it often does not emerge as significant on its own. As an example the inverse relationship with HDL often renders the effect of TG in multiple risk estimations when HDL is added. Nevertheless, TG is today categorized as an independent risk factor, and certain lipid rich VLDL remnants are considered atherogenic (35). There are several possible reasons to an increase in TG, but the most common are overweight/obesity and physical inactivity (36-38).

Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol, thus consists of all apo B containing lipoproteins. Epidemiological studies from Denmark have shown that this remnant cholesterol is a better predictor for total mortality than is LDL cholesterol (39). With low TG, LDL makes up most of the non-HDL fraction, hence there will be a correlation between the two, and non-HDL contributes with limited extra information. With higher TG on the other side, for instance at the level of 2.5-5 mmol/l, this correlation is less pronounced, and non-HDL might be a more precise measure of the whole atherogenic load than LDL alone (39).

Lp(a) has been indicated as a causative factor of premature death, after the finding of a strong association between high Lp(a) levels and increased CVD risk (40). A frequently used reference value in the clinic is < 300 mg/l as levels above this has been associated with an increased risk of CVD (41).

C-Reactive Protein (CRP) is an indicator that differentiates a pathological inflammatory process in the body from normal biological processes. Micro-CRP (mCRP) is a highly sensitive assessment of CRP of the lowest measurement range. Inflammation will increase the CVD risk by contributing to an acceleration of the atherosclerotic process. This has also been shown among patients with normal lipids but who are suffering from inflammatory diseases (42). Statins reduce plasma mCRP by 20-30 %. Patients with a low mCRP during treatment, have a better clinical outcome independently of LDL cholesterol level. The JUPITER trial concluded that persons with both LDL lower than 2,0 mmol/l and CRP lower than 2,0 mg/l had the lowest CVD event rate (43).

Smoking

The INTERHEART study found smoking to account for 36 % of the PAR. There has been established a dose-response relationship between the number of cigarettes smoked and risk of non-fatal acute MI. Smoking affects both the hemodynamics, the development of atherosclerosis, and creates a pro thrombotic environment increasing the risk of pathological thrombosis and plaque rupturing (44, 45).

Smoking has been confirmed as a significant risk factor in FH patients (46). It causes an increased oxidative harm to circulating LDL particles and also a reduction in vasodilatation, which altogether highly contributes to the atherosclerotic process. As FH affected individuals have a much higher number of LDL particles available for oxidation, this potentially results in a higher number of macrophage engulfed particles, leading to more foam cells, hence speeding up the plaque development. Further, the smoking will also reduce the HDL level, contributing to a reduced reverse LDL-transport. The risk for CVD events is multiple higher for a smoking FH patient, than for a non-smoking non-affected individual, both for men and for women (47). Passive smoking has also been shown to increase the risk of cardiovascular mortality, and this can be a great problem for problem for the FH children (48).

About 13 % of the Norwegian men and 14 % of the women were daily smokers in 2014. In addition 9% of the population stated that they are occasional smokers. Smoking is reduced in the population as a whole from 26% to 13 % over the ten last years (49).

Stress

Depression predicts CVD risk in young healthy people in perhaps a dose response relationship manner (50), and the INTERHEART study found stress to account for 33 % of the PAR. The Whitehall study found that those who felt the least in charge of their work had the highest rates of heart disease (51). Stress and depression might give people less energy to focus on health, hence being prone to lead an unhealthier lifestyle. The stress in itself can lead to physiological changes that may affect the heart health. Decreased blood flow to the heart muscle, triggering of an irregular heart beat and increased blood clotting are effects from stress, that over time may cause damage on the blood vessels, increasing the risk of atherosclerosis (52). A stress related increase in blood pressure will be a part of this (53).

Abdominal obesity

Abdominal Obesity is an established risk factor for CVD, and was found in the INTERHEART study to account for 20 % of PAR. Intra-abdominal fat has a significant impact on our metabolism, and has been associated with glucose intolerance, insulin resistance, hypertension, physical inactivity, dyslipidemia and increased inflammation (54-56). Abdominal obesity and several of these factors are closely linked to the metabolic syndrome, defined as: “an increased abdominal circumference (≥ 94 cm men and > 80 cm in women of European descent) in combination with at least two of four metabolic features such as serum triglycerides ≥ 1.7 mmol/l, HDL cholesterol < 1.0 mmol/l in males, or < 1.3 mmol/l in females, blood pressure > 130 mm Hg systolic or > 85 mm Hg diastolic or BT treatment, fasting plasma glucose ≥ 5.6 mmol/l or diabetes treatment” (57). Patients with metabolic syndrome have been found to have significantly higher rates of coronary, cardiovascular, and all-cause mortality (58).

Hypertension

Hypertension was found to account for 18 % of the PAR in the INTERHEART study. It is defined as having a systolic blood pressure (SBP) above 140 mmHg, and has a continuous and graded relationship to the risk of CVD, although this relationship changes with other risk factors present. The Framingham study found that even at only high-normal blood pressure (SBP 130-139 mm Hg, diastolic blood pressure (DBP) 85-89 mm Hg, or both) increases the risk of CVD 2-fold, as compared with healthy individuals (59). In a global perspective, hypertension is estimated to account for 54 % and 47 % of all strokes and ischemic heart disease events for respectively, making it the single biggest risk factor for stroke (60).

Diet

Diet is characterized as an intermediate risk factor which is affecting several of the major risk factors of CVD, such as serum cholesterol, hypertension and BMI. A diet with a low intake of fruit and vegetables was in the INTERHEART study assessed to account for 14 % of the PAR.

A high intake of fruit and vegetables is a characteristic of several dietary patterns found to be CVD friendly; such as the vegetarian diet, the prudent diet and the DASH diet, where the latter improves the risk of high blood pressure (61). Still, ever since the classical seven

countries study (33), the Mediterranean dietary pattern has been of particular interest. It has consistently been associated with a reduction of CVD risk, and it is ranked as the most likely dietary pattern to provide protection against CVD (62-64). It is characterized by a high intake of plant foods such as fruits, vegetables, cereals, beans, nuts and seeds, and the use of olive oil as the primary source of fat, and has a low regular consumption of alcohol. Dairy products, fish and poultry is consumed in moderate amounts, and red meat is consumed only in low amounts. This results in a rather low intake of saturated fatty acids, typically in the range below 10 energy % (65).

At the Lipid clinic the main advices given is to eat less fat, especially saturated fatty acids, replace the saturated fat with unsaturated fat, and to eat more vegetables, fruit and foods rich in fibers daily, in addition to increasing the fish consumption. A low consumption of alcohol and sugar-rich foods and liquids is also recommended, especially if the patients have overweight, high triglycerides or diabetes.

Åkesson et al has recently found that a low risk diet rich in fruits, vegetables, legumes, nuts, reduced fat dairy products, whole grains and fish in a combination with a moderate intake of alcohol was associated with a 35 % reduction of primary MI compared to a high risk group. When they combined this with other low-risk lifestyle behaviors like non-smoking, being physically active and avoiding abdominal adiposity, the risk was lowered by 86 % (66). As many of the adult FH patients have troubles reaching their treatment target, this illustrates the essence of a combination of both medical treatment and a healthy lifestyle.

Physical activity

Physical activity reduces the risk of CVD and at least 30 other various health conditions and diseases, including the other CVD risk factors such as hypertension and DM (67). In addition to improve insulin resistance and lowering blood pressure, the cardio protective features of exercise and general physical activity include reducing adipose tissue, improving lipid profile and lowering vascular inflammation, only to mention a few (67). The lack of physical activity was in INTERHEART found to account for 12 % of the PAR, and the Norwegian health authorities recommend a minimum of 150 minutes of moderate intensity per week, or a minimum of 75 minutes of high intensity exercise for adults (68). This frequency of activity has been associated with a 30 % reduction in vascular events (69).

A sedentary lifestyle has become very prevalent. Total sedentary time is shown to be associated with poorer insulin sensitivity (70). A large metaanalysis have shown that prolonged sedentary time was independently associated with deleterious health outcomes regardless of physical activity. Significant hazard ratio associations were found with all-cause and cardiovascular disease mortality and incidence and cancer mortality and incidence, and type 2 diabetes incidence (71).

Diabetes Mellitus

In 2014 about 9 % of all adults had DM, and T2DM is the most common form, representing about 90 % of all cases (72). Diabetes mellitus is characterized by either an insufficient insulin production in the pancreas, or a lack of ability to use the insulin it produces, both leading to abnormalities in almost the entire metabolic system (73). In the WHO Multinational Study of Vascular Disease in Diabetes, CVD was found to be the cause of approximately 50 % of all deaths of individuals with DM (74), and the INTERHEART study found DM to contribute with 10 % of the PAR. DM will have both micro and macro vascular complications, manifested as nephropathy, neuropathy, retinopathy and atherosclerosis, potentially resulting in kidney failure, amputation, blindness and CVD. The greatest prevention and reduction in T2DM is achieved through lifestyle changes especially concentrated on diet and increased exercise (75). The Diabetes Prevention Study found a 58 % reduction in T2DM incidence through lifestyle intervention (76).

Diabetes is diagnosed by the criteria of having a fasting plasma glucose of 7,0 mmol/L or higher, and or a plasma glucose of 11.1 or higher 2 h after 75 g glucose load (73).

Alcohol consumption

The association between alcohol and CVD is illustrated through a J shaped curve where a regularly low intake seems to have some protective effect (77) potentially through elevated HDL and a vasodilating effect, while most studies have found that higher alcohol consumption increases the CVD risk (78). The INTERHEART study found excessive drinking to account for 7 % of the PAR, and an episode of heavy drinking is associated with an increased risk of acute MI in the subsequent 24 hours, particularly in older individuals (18).

1.3.4 Medical treatment

Many HeFH patients will need a triple medication consisting of high intensity statin together with ezetimibe and a resin. In Europe the traditional LDL targets are lesser than 2,5 mmol/l or lesser than 1,8 mmol/l in primary and secondary prevention, respectively. If that cannot be reached, a secondary treatment target of a LDL reduction of more than 50% can be accepted (79). The new American guidelines from AHA/ASC 2013 have evaluated the latter treatment target, and accepted the LDL reduction of more than 50% as the main treatment target. Side effects and intolerance determines choice of type and intensity of lipid medication.

In Norway, patients suffering from homozygote FH are usually treated with weekly LDL-apheresis in combination with high intensity statin and ezetimibe. The effect of statin is dependent of the patient having a rest LDLR function. Also some individuals with HeFH are treated with LDL-apheresis. This is often due to statin intolerance resulting in very high LDL values, and especially if the patient has serious CVD as well.

Types

Statins are considered to be the first-line pharmacological therapy for reducing LDL levels, which can be reduced with approximately 20-55 % depending on type and dose (27, 80).

Statins inhibit the pathway of cholesterol synthesis through selective competitive inhibition of HMG-CoA reductase, the rate limiting enzyme of this pathway. As a consequence, not only is the intrinsic cholesterol production down regulated, but there is also an upregulation of LDLR expression through a shift in activated transcription factors. As a consequence more LDL particles are removed from the blood, and the blood cholesterol falls (81).

There are seven different types of active substances, here sorted by the maximum reduction of LDL: Rosuvastatin, atorvastatin, simvastatin, pitavastatin, lovastatin, pravastatin and fluvastatin (81).

Ezetimibe is a selective inhibitor of the transport of cholesterol and plant sterols over the small intestine mucosa. It decreases the uptake both of the ingested cholesterol from foods and the synthesized cholesterol from bile acids in the liver (82). Ezetimibe reduces serum total cholesterol with an add on effect to a statin (83). It also reduces the LDL, apo B, and TG as well as increases HDL in the circulation, all without affecting the level of fat-soluble

vitamins (84). Since the mechanism of action is different from that of the statins, the combination of the two will function well.

Colesevelam is a non-absorbed bile acid sequestrant. It works through binding the bile acids in the intestine, inhibiting them from being reabsorbed into the enterohepatic circulation. As a consequence, the liver has to produce new bile acids (85). Since the bile acids are synthesized from cholesterol, the uptake of circulating cholesterol is increased through upregulation of LDL receptors on the hepatocytes. The use of colesevelam might affect the absorption of fat soluble vitamins, and should be taken into consideration during the treatment (86).

Niacin, or vitamin B3, has several functions in the human body. When consumed in larger doses, it increases the level of HDL and apo A1 in the circulation, as well as lowering apo B containing lipoproteins. It is thought that the HDL effect is facilitated through an inhibition of HDL removal from the circulation. The effect on apo B lipoproteins is a result of a modulation of TG formation that leads to decreased circulating VLDL and LDL (87), as well as an increased clearance of apo B (88). It also inhibits lipolysis in adipocytes which decrease the circulating TG (89).

This is the oldest lipid-lowering drug, used for nearly 50 years, and can potentially reduce LDL cholesterol levels up to 20%. Although, it is now in very limited use in Norway due to increased serious side effects and no CVD treatment effect when combined with statins (90, 91). It is now only used by a few FH patients who handle the side effect of flushing.

Fibrates are PPAR α agonists that will stimulate the lipid- and glucose metabolism through regulation of gene expression. They increase the level of HDL through upregulation of apo-AI and apo-AII gene expression, as well as reducing TG considerably and LDL moderately. Like niacin, fibrates have been used for several decades, and has in the same manner not been found to have any significant effect on primary or secondary CVD endpoints when combined with statin (91). However, there was an effect on secondary CVD endpoint in a post hoc subpopulation in the study with metabolic syndrome and increased TG. Fibrates are therefore at rare occasions used by patients with FH and FCH, when they exhibit serious statin intolerance and especially if they reveal combined hyperlipidemia.

The main indication of use of omega 3 in Lipid clinics is considerably increased TG, due to its TG lowering capacity (92). The reduction of TG is accomplished through both a decreased

hepatic production as well as an increased clearance of TG from the circulation (93). Omega-3 can also exert an anti-arrhythmic effect, decrease the heart rate and hypertension, and decrease platelet aggregation (94). Omega-3 is suitable to combine with all other lipid-lowering agents. There have been conflicting results on the effect on CVD risk from omega-3, but several randomly controlled clinical trials have found an association with a decreased CVD risk (95-97). Among the FH patients, omega-3 fatty acids are used for reducing elevated triglycerides, and especially if the patient has experienced a CVD event.

Due to the high baseline cholesterol in FH patients, statin treatment alone is not enough to reach the treatment target, or they can experience side effects on higher doses of statins. Thus there is a need for combination treatment, as it both gives an additive lowering effect and might allow for a lower statin dose to be used. “The statins’ rule of 6” advocates that a doubling in statin dose only adds an extra LDL lowering of 6 %. But adding ezetimibe to 10-20 mg of statin will be equally effective as 80 mg statin monodose (98).

There has been documented a significant effect from the combined treatment of statin and ezetimibe on a broad combined primary endpoint, consisting of different types of CVD and stroke (98, 99). There has also been a prospective randomized study with the use of statin, ezetimibe and coleselam versus statin and ezetimibe (100).

In RCTs the frequency of side effects and intolerance for statins are relatively low. But in a clinical setting where the patients use the highest possible doses of statins, ezetimibe and resins, side effects will often be a limiting factor for the intensity of dosages and type of medication. Large register studies have revealed that statin treatment is associated with the whole specter of muscular pains, (101, 102) An autoimmune necrotizing myositis is well documented (103), but is so far fortunately seldomly reported. The statins are slightly diabetogenic, and may also increase the liver transaminases (104). Some patients also endure gastrointestinal troubles such as discomfort, diarrhea and borborygmi (105).

2 Aim of the study

The Treat To Target Familial Hypercholesterolemia (TTTFH)-study is an assessment of the treatment of the FH patients at the Norwegian Lipid clinic, Rikshospitalet, Oslo University Hospital (OUS) -the largest and leading Lipid clinic in Scandinavia. We wish to describe the effect of a maximally aggressive lipid lowering treatment by following a prospective protocol in a structured manner, and further investigate what is possible to achieve through maximal use of medication and lifestyle intervention in a real life setting, monitored over eight years. We look at the medication, and the habits of diet, smoking, physical activity and alcohol consumption, in addition to how the patients value lifestyle, to have low cholesterol and side effects. We further evaluate the lipid parameters and the achievements of lipid treatment targets as stated by the international recommendations, and the occurrence of CVD in the sample. In our study population, 20 patients have experienced at least one CVD event. We wish to investigate whether there are any immediate differences in what characterize those with CVD compared to the 44 who have not had a CVD event, concerning the same parameters as above.

2.1 Study objective

2.1.1 The specific objectives in this study

Specific objectives with this thesis are:

1. To follow the FH population over time to measure changes resulting from high intensive treatment from 2006 to 2014 concerning:
 - a. Investigate to what extent the patients reaches their lipid treatment targets
 - b. If and how the lifestyle factors smoking, physical activity, alcohol consumption and diet have changed during the observation time.
 - c. Describe types and intensity of medication and the occurrence of medical side effects at Visit 3 (V3).

- d. Occurrence of CVD and unfavorable comorbidities such as T2DM and hypertension, in addition to changes in BMI, weight and waist circumference.
 - e. Investigate the patient's preferences of:
 - I. an intensive lifestyle improvement versus an intensive lipid medication, and
 - II. how they value having a low cholesterol level versus suffering from medication side effects.
2. To describe what characterizes the patients who have suffered from CVD compared to the patients who have not, concerning:
 - a. Lipid values and other blood parameters.
 - b. Occurrence of lifestyle factors as a low Smart Diet score, smoking, alcohol consumption and inactivity
 - c. Severity of lipid medication and side effects
 - d. Occurrence of diabetes mellitus type 2 and hypertension

2.1.2 Hypothesis

The specific hypothesis of this thesis is that an intensified treatment program and achievement of the treatment targets results in a lowered CVD risk.

3 Subjects and methods

The master thesis was approved by The Regional Committee of Medical Ethics (appendix 1).

3.1 Recruitment of participants

From the 9th of January 2006 to the 9th of July 2006, 426 adult patients (i.e. 18 years or older) with verified or probable FH were continuously invited to participate in the TTTFH project by the consultants at the Lipid clinic during the routine consultation visits. They were not to participate in other projects, be able to fill out the questionnaires, receive LDL apheresis, or be off medication due to pregnancy, breast feeding or any other non-representative reason to their normal medication state. For the patients who agreed on participation (n=357), this consultation would serve as the first visit (V1) in the study. Of the patients who were not included, 43 did not wish to or could not participate and 26 did not meet the inclusion criteria. Data were collected through an ordinary medical examination and documented by the patients' records, and by three questionnaires and schemes; A Doctor's scheme (appendix 2), dealing with medical data that was filled out by the doctor during the consultation; the Smart Diet (appendix 3) and the Patients' Preferences scheme (appendix 4). The two last forms were both filled out by the patient upon the arrival at the Lipid clinic. The three questionnaires are further described later in the Collection of Data-section. Fasting blood parameters were regularly taken during the weeks before the visits, or if missing, taken at or soon after the visits. Anthropometric data were taken at site during consultation for most patients, but a few are self-reported. The study was during 2006 considered to be a quality assessment study, and therefore needed no approval from the Regional Ethical Committee.

Visit 2 (V2) was conducted as a follow up median one year after V1, during 2007. All participants from V1 were routinely recalled for a new consultation in the Lipid Clinic, and 332 patients wished to further participate in the TTTFH-project. Of the 25 patients who were not included, 13 did not wish to or could not participate, 7 did not meet for consultation and 5 did not meet inclusion criteria. Questionnaires, schemes and measurements were collected according to the same procedure as for V1, all except the Patients' Preferences scheme that was not included in this round. Data from the first 110 patients were during 2007 entered into an especially made ACCESS lipid database. Some carefully chosen variables on 110 of these patients were transferred to SPSS data files to make up a preliminary impression of the

situation, and the results were presented as an oral presentation at European Atherosclerosis Society especial symposium the 27th of April 2008. These 110 patients form the basis for the continued work presented here from the Visit 3 (V3).

The evaluations at V3 constitute the clinical work of this master thesis. V3 was conducted from early August to late December 2014. Of the 110 patients from V2, two patients were dead; one female from cancer and one male from ACS. Out of the 108 remaining subjects, only 78 were still scheduled at the waiting list of the Lipid clinic. They were invited by a summon (appendix 5) that was sent to their hospital registered addresses. The invitation consisted of the ordinary consultation summon, information concerning the study, implications of participation, and a written consent which the patients were asked to sign and bring to their scheduled V3 at the Lipid clinic. The 30 patients, who were no longer registered patients at the outpatient clinic, was telephoned to examine their wish for continuing as participants in the TTTFH-study. If interested, they were temporarily activated as a patient at the lipid clinic, and received the invitation letter at their hospital-registered address. Questionnaires, schemes and measurements were collected according to the same procedure as for V1. The clinical consultations were conducted by one doctor and a clinical nutrition master student, trained by the in house clinical nutritionist. Specific data were collected by the same person to prevent information bias. We managed to recruit 68 of the patients, and 67 completed their combined doctor and master student consultations from the 13th of October until the 18th of December of 2014. Finally 64 patients were included in the final patient sample of V3; 31 females and 34 males in total. Of the 36 patients who were not included, 25 did not wish to or could not participate, or was not reached, 7 did not meet for consultation and 4 did not meet inclusion criteria. Figure 2 illustrates the flowchart of the three visits.

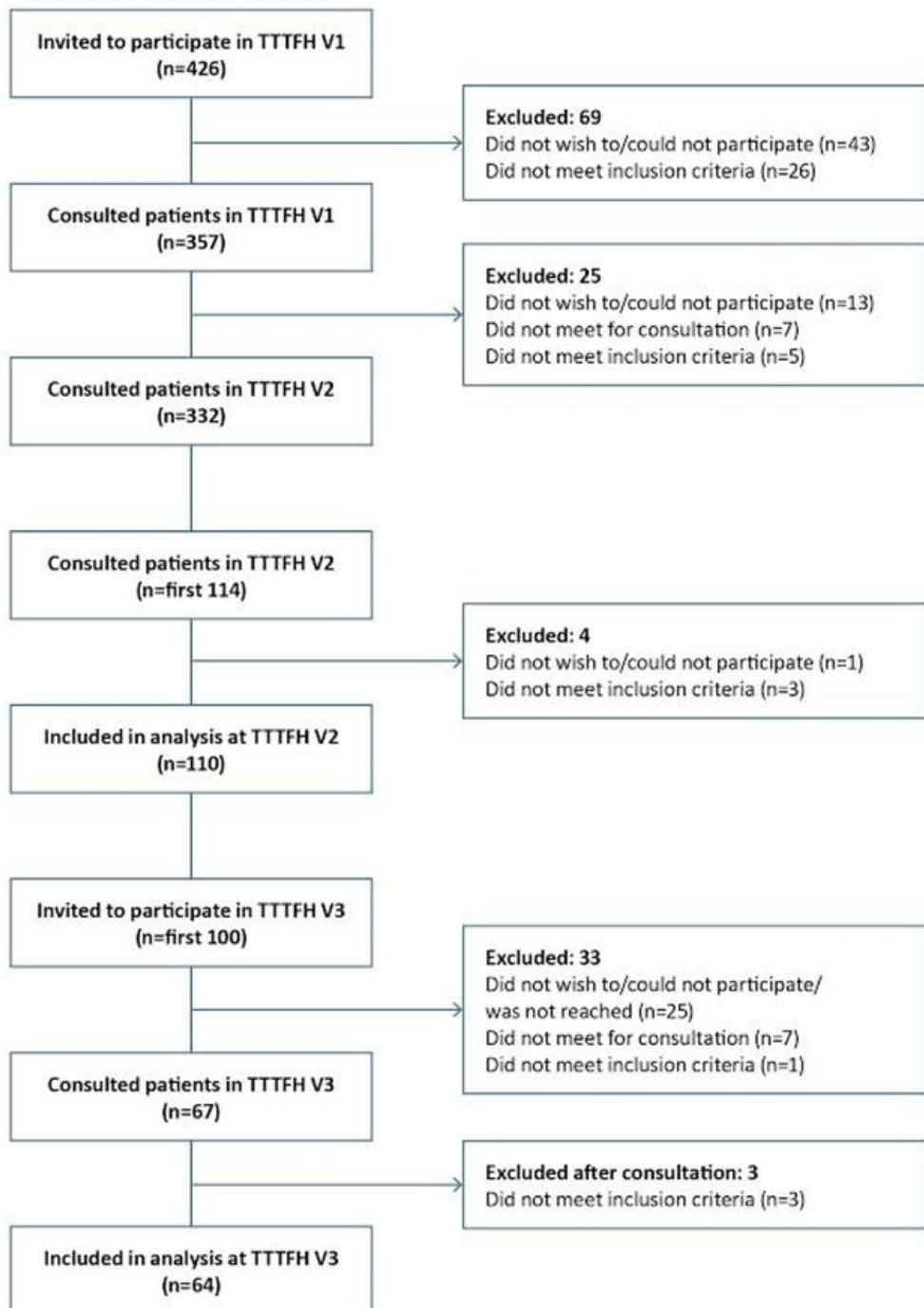


Figure 2. Flow chart showing inclusion and exclusion of the FH subjects. V1 was conducted in 2006, V2 in 2007 and V3 in 2014.

3.2 Materials

3.2.1 Collection of data

Any missing information was collected during V3 from the medical records to the furthest extent possible.

Blood parameters

The following blood parameters were sampled in nearness in time or at each of the three visits. The results were later collected from the medical records and the laboratory system for TC, LDL-C, HDL-C, TG, apo B, apo A1, CRP, fasting glucose and HbA1c. Lp(a) was most often only measured once for each patient, and was collected from older medical records. The untreated TC values were mostly reported from the notes of the referring physicians. We refer to V0 for the time point of the first known untreated TC value. Apo B/apo A1-ratio and non-HDL cholesterol was calculated in SPSS based on the given values. Most patients used the pre-filled laboratory requisition sent to them from the Lipid clinic. The blood samples were collected at their local hospitals or at their private doctors. The patients were encouraged to be 12 hours fasting at the blood takings. If the patient had no blood analysis in beforehand, it was sampled at the Lipid clinic at the day of the visit, or few days later. Most of the analyses were performed at Biochemical Laboratory Department at Rikshospitalet, OUS. Some analyses were performed at the local hospital or at private medical laboratories.

Medication, Side effects and Potential endpoints

The Doctor's scheme was developed for this study, and consists of three pages. The first page concerns the type and doses of medication with dates of changes. It also describes types of medical side effects as experienced by the patients, and a probability evaluation of these complaints as being medical side effects, as evaluated by the doctor. The doctor also states if he intensifies the lipid medication, or the reasons for not doing so. The second page addresses lifestyle, complementary to the Smart Diet questionnaire. The third page collects the adverse events, and these are not evaluated in this study. The fourth page addresses the potential endpoints.

The doctor has filled out the forms during the consultation. The first form/scheme lists the patient's medications, dose and time of usage. It continues with a doctor's assessment of whether there is "no", "possible", "probable" or "definite" side effects from the medication, the type of side effect, and if the medication is intensified, and the reason if not. The fourth form/scheme maps whether the patient has suffered from a CVD event since the last visit, what type and at what time point.

Statin therapy was categorized according to intensity (79). High intensity statin therapy is defined as Atorvastatin 40-80 mg or Rosuvastatin 20-40 mg. Moderate intensity statin therapy is defined as Atorvastatin 10-20 mg, Rosuvastatin 5-10 mg, Simvastatin 20-40 mg, Pravastatin 40-80 mg, Lovastatin 40 mg, Fluvastatin 40 mg or Pitavastatin 2-4 mg. All the statin doses were taken daily in one dose. Ezetimibe dose was 10 mg for 100 % of the users. The Colesevelam dose was 3750 mg, which is the maximum doses, for almost all patients.

Lifestyle

The Smart Diet questionnaire has been developed by the Lipid clinic, and it is validated for all ages (106). The questionnaire has been in daily use at the Lipid Clinic for many years, and has been improved by several revisions. We use the version from 2003 for all three visits. It allows the doctors and clinical dieticians to get a quick overview of how "heart friendly" the patient's diet is, as well as hints of areas of improvement. Fifteen questions are answered and scored from one to three points with a total maximum score of 45 points. The score is calculated by hand during the consultation. The Smart Diet total score will then be categorized into one of three main categories, defined as low if the score is 29 or lower, medium if between 30 and 37, and high if 38 or higher. The scheme also covers weight and height, and other lifestyle factors such as level of physical activity, smoking and dietary supplements. At V3 waistline circumference and BMI was added manually, and the anthropometrical data was taken at site with the same measuring equipment.

We intended to estimate to what degree and extent the patients choose low fat dairy and lean meat products, and how often they consume fish, vegetables and fruits. By summing up the relevant questions from the Smart Diet, these four categories were made.

Four questions (no 1,2,4 and 5) concerning the patients choice of dairy products in the Smart Diet were added together into one category that sums up whether the type of milk, sour cream

etc., cheese and butter they use are of whole fat, medium or low fat type. This resulted in a dairy category with a maximum score of 12. The question on the use of oil versus ordinary butter in cooking and frying was left out. The reason for that was that many patients today might use coconut oil, containing a high content of saturated fats. We could therefore not assume with certainty that the patients who “used oils for cooking and frying”, used monounsaturated vegetable fat.

Two questions in the Smart Diet (no 6 and 9) describe the choice of meat for dinner or on sandwiches as lean, medium or fat. These were extracted and added together, and yielded a meat category with a maximum score of six.

In the same manner two questions (no 7 and 10) on how often they eat fish for dinner or on their sandwiches, were added together and resulted in a maximum possible fish score of six. The alternatives were quantified. For fish for dinner the categories was quantified into “once per week or never”, “two times per week”, and “three or more times per week”. For fish on sandwiches the three alternatives were “once per week or less”, “two to four times per week”, and “five or more times per week”.

Lastly, one question (no 12) asked how often they eat vegetables, and one question (no 13) asked how often they eat fruit, Both these questions have a possible maximum score of three, and were categorized into how many units ingested per day, and split into “one unit or less per day”, “two units per day”, or “three or more units per day”. One unit is defined as one handful or approximately 150 grams.

The patients pre-registered the Smart Diet questionnaires when sitting in the Lipid clinic waiting room before the consultations. The scheme was used as the base for a semi-structured discussion with the patient and either the doctor or a clinical dietitian at V1 and V2. At the actual V3 the master student performed a structured interview. Some of the scores were modified during the consultation, and both the patients’ original score and the corrected score were registered. The patients’ unmodified score were used as far as possible. If the patient had crossed for more than one alternative, we calculated a mean score of the two. In cases of missing answers, the total score has not been calculated. At V3 the clinical nutrition master student also recounted the total score for all available Smart Diet questionnaires from all visits, as a control.

In the Smart Diet questionnaire smoking was grouped based on how many cigarettes were smoked daily: “don’t smoke”, “five or less”, “six to ten”, “eleven or more”, or “party smoker”. Physical activity was categorized as “never”, or how many times per week they worked out for more than 30 minutes per week: “less than once”, “once to twice”, “three or more”. The physical activity was also categorized into “high intensity”, “medium intensity” or “a combination of the two”. The alcohol consumption was categorized as “never”, or how many units of alcohol consumed per week: “less than one”, “one to seven”, “eight to fourteen” or “fifteen or more”. Dietary supplements were categorized into cod liver-oil, omega-3 capsules, multivitamins and others.

Patients’ preferences

The Patients’ Preferences questionnaire is a non-validated questionnaire developed at the Lipid clinic for this study. It focuses on how satisfied the patients are with the treatment offered at the Lipid clinic, and further investigates some of the patients’ attitudes towards different statements. We chose to only focus on the three most relevant questions in this thesis. The first is whether the patient considers “lifestyle improvement to be equally important as the use of lipid medication”. The second question asks whether the patient “wishes his or hers cholesterol level to be as low as possible”. The third question asks if the patient “considers it to be more important to have little of side effects from medication than a low cholesterol level”. They were all divided into an ordinal scale from “fully agree”, “partly agree”, “neither nor”, “partly disagree” and “fully disagree”.

3.2.2 Statistical methods

For all data analysis the statistical program IBM SPSS version 22 was used. To control for plotting errors we checked the datasheets for random selected variables, as well as running descriptive analysis and carefully double-checking continuously during the plotting process. This thesis is mainly a descriptive analysis of the treatment program given at the Lipid clinic in Norway from January 2006 until the end of 2014. Results are mainly given for the population as a whole and for the group of patients who have developed CVD versus those who have not.

A $p < 0.05$ was considered statistically significant. For all analyses, the upper limit for a tendency of difference was put at $p < 0.1$.

All data were checked for normal distribution by histograms, normal Q-Q-plots, detrended Q-Q-plots. If the continuous variables concerning the population as a whole were normal distributed, they were firstly explored, and then analyzed with paired t-tests. If the data were found not to be normal distributed, nonparametric tests were used, more specifically paired Wilcoxon signed ranks test, to analyze V1 against V2, V2 against V3 and V1 against V3. If there was any uncertainty concerning the normal distribution, non-parametric tests were used.

For categorical variables, frequency analysis and cross tabulation were done. To calculate the p-value, paired Wilcoxon signed ranks test were used to analyze V1 against V2, V2 against V3 and V1 against V3.

For the CVD vs non-CVD analysis the same routine was followed, except when calculating whether the differences was significant. As the number of CVD patients was only 20, we used non-parametric analysis only, as recommended by Altman (107). For this the 2 independent samples Mann Whitney U test was used.

All collected data was entered into SPSS-datasheets. Missing data was handled by giving it a blank cell in SPSS.

4 Results

4.1 Comparison of CVD risk factors at baseline and 8 years after

4.1.1 Characterization

The characterization of the 64 subjects is shown in table 1. The mean age of the study population was at V1 in 2006 44.2 years, with 29 females and 35 males. The mean age at V3 in 2014 was 52.1 years. FH mutation was confirmed for 57 (89.1 %) patients, 4 (6.3 %) were considered clinical probable and 2 (3.1 %) possible FH, and 1 categorized as polygenic hypercholesterolemia.

There has been a slight reduction in the patients' weight and BMI from V1 to V3, which was significant ($p<0.001$). Further, we found a significant reduction in the BMI from V1 to V2, and simultaneously a significant increase in weight. As this is conflicting data and we have used pairwise exclusion in the statistical calculations, it looks as the explanation might be due to the use of medians. When using the mean values, both the weight and the BMI parallel with each other, and have increased slightly from V1 to V2. On V3 there were one (1.6 %) underweight woman, 14 (21.9 %) women and 11(17.2 %) men with a normal BMI, 8 (12.5 %) women and 14 (21.9 %) men were overweight and 6 (9.4 %) women and 10 (15.6 %) men were obese (data not shown).

The mean of the waist line-variable have been quite stable at all three visits. Unfortunately we only have measurements for 19 and 43 subjects at the two first visits respectively, hence missing 70.3 % at the most, and therefore give descriptive data only. The median waistline circumference was 97.4 cm and 87.9 cm for men and women respectively, above the recommendation for both sexes.

There were as many men as women who express a desire to reduce their weight at all three visits, and where in the interval of 60 to 70 % for both sexes (table 2).

At V3 the CVD risk factors hypertension and DMT2 was found among 22 (34.4 %) and 6 (9.4 %) respectively. The number of patients who suffered from one or more CVD events at V1

was 15 (23.4 %). Eight years later at V3, the number had increased to 20 (31.3 %). Of all the 20 patients 7 have had one or more myocardial infarctions (MI) and 2 had one or more transient ischemic attacks (TIA). Further, 11 had had one or more percutaneous coronary interventions (PCI), and 7 had done one or more coronary artery bypass grafting (CAGB) operations. Another 10 patients have documented angina pectoris (AP), and further two was categorized as uncertain AP. Two had an aorta aneurism, 6 had a documented carotis stenosis, including 50 % asymptomatic stenosis. Three are registered with uncertain claudication intermittens and 1 with blocking of peripheral vessels. Three had an implanted ICD and 3 an implanted valve.

All reported data of the patient's medication are from V3. A major portion 54 (84.4 %), of the patients, are receiving high intensive statin therapy. Only 8 (12.3 %) were using medium intensity statin therapy, probably because of either side effects of statins or not needing higher doses due to an already reached treatment targets. There were 2 (3.1 %) patients that did not take statins for several months before V3, one due to fear of side effects, the other was non-compliant with no given reason. Ezetimibe was used by 51 (79.7 %) mainly in addition to statin therapy. Colesevelam was used by 19 (29.7 %) at a dose of 3750 mg or more, mainly in addition to statin therapy.

The number of patients that used dual lipid medication (statins and ezetimibe) was 33 (51.6 %), while 18 (28.1 %) of the participants used triple lipid medication, i.e. receiving a statin, ezetimibe and colesevelam. Of all patients receiving cholesterol-lowering medications 2 (3.1 %) had certain, 16 (24.6 %) had probable and 6 (9.2 %) had possible side effects, all assessed by the investigating doctor.

Table 1. Clinical characterization of the subjects on V1, V2 and V3.

Total n=64	V1	V2	V3	p-value ² V1-V2	p-value V2-V3	p-value V1-V3
	n ¹	n	n			
Age (år)	64 44.2 (41.1-47.3)	- -	64 52.1 (49.0-55.3)	- - -	- - -	- - -
Female (%)	29 45.3	- -	- -	- -	- -	- -
Male (%)	35 54.7	- -	- -	- -	- -	- -
Height (cm)	56 173.2 (171.0-175.6)	58 173.4 (171.3-175.5)	64 172.4 (170.3-174.5)	- - -	- - -	- - -
Weight (kg)	55 79.0 (52.4,135.0)	59 80.0 (53.0,144.0)	64 78.4 (48.1,140.0)	0.030	0.946	0.295
Waist (cm)	19 94.0 (78.5-126.0)	43 92.0 (65.0-128.0)	59 94.2 (65.0, 142.0)	0.049	0.839	0.113
<i>Men</i>	- -	- -	32 97.4 (80.8, 142.0)	- - -	- - -	- - -
<i>Women</i>	- -	- -	27 97.9 (65, 108.7)	- - -	- - -	- - -
BMI (kg/m ²)	55 26.7 (17.8,39.3)	59 26.5 (18.4,40.9)	64 25.5 (18.3,42.1)	0.027	<0.001	<0.001
Genetical verified FH	- -	- -	57 87.7	- - -	- - -	- - -
Clinically probable FH	- -	- -	4 6.2	- - -	- - -	- - -
Clinically possible FH	- -	- -	2 3.2	- - -	- - -	- - -
Cardiovascular risk factors	- -	- -	- -	- - -	- - -	- - -
<i>Hypertension</i>	- -	- -	22 34.4	- - -	- - -	- - -
<i>Diabetes Mellitus</i>	- -	- -	6 9.4	- - -	- - -	- - -
Cardiovascular disease	- -	- -	64 20 (31.3 %)	- - -	- - -	- - -
<i>One or more MI</i>	- -	- -	64 10 (15.6)	- - -	- - -	- - -
<i>Angina Pectoris</i>	- -	- -	64 10 (15.6)	- - -	- - -	- - -
<i>One or more PCI</i>	- -	- -	64 11 (7.2)	- - -	- - -	- - -
<i>CAGB</i>	- -	- -	64 7 (10.4)	- - -	- - -	- - -
Medication	- -	- -	- -	- - -	- - -	- - -
<i>High intensity statin therapy</i>	- -	- -	64 54 (84.4)	- - -	- - -	- - -
<i>Moderate intensity statin therapy</i>	- -	- -	64 8 (12.5)	- - -	- - -	- - -
<i>No statin therapy</i>	- -	- -	64 2 (3.1)	- - -	- - -	- - -
<i>Ezetimibe</i>	- -	- -	64 51 (79.7)	- - -	- - -	- - -
<i>Colesevelam</i>	- -	- -	64 19 (29.7)	- - -	- - -	- - -
<i>Dual lipid medication</i>	- -	- -	64 33 (51.6)	- - -	- - -	- - -
<i>Triple lipid medication</i>	- -	- -	64 18 (28.1)	- - -	- - -	- - -
Side effects (certain and probable/possible)	- -	- -	64 18/6 (28.1/9.4)	- - -	- - -	- - -

Data are given/presented as mean (95 % confidence interval), median (min, max) or number of individuals n (%).

¹n indicates total number of total measured individuals.

BMI=Body Mass Index; FH=Familial Hypercholesterolemia; DM=Diabetes Mellitus; MI=myocardial infarction;

Dual lipid medication = both statin and ezetimibe.

Triple lipid medication = statin, Ezetimibe and resin.

Height measured on V3 was used for calculation of BMI on all visits.

High intensity statin therapy is defined as atorvastatin 40-80 mg or Rosuvastatin 20-40 mg. Moderate intensity statin therapy is defined as Atorvastatin 10-20 mg, Rosuvastatin 5-10, Simvastatin 20-40 mg, Pravastatin40-80 mg, Lovastatin 40 mg, Fluvastatin 40 mg or Pitavastatin 2-4 mg.

²Wilcoxon signed ranks test with pairwise exclusion was used to calculate p-values

Table 2. Number of subjects who wish to reduce weight

	V1		V2		V3		p-value ¹ V1-V2	p-value V2-V3	p-value V1-V3
	Women	Men	Women	Men	Women	Men			
Yes (%)	15 (60.0)	19 (63.3)	14 (58.3)	19 (61.3)	18 (66.7)	21 (61.8)	-	-	-
No (%)	10 (40.0)	11 (36.7)	10 (41.7)	11 (35.5)	9 (33.3)	13 (38.2)	-	-	-
Do not know (%)	-	-	-	1 (3.2)	-	-	-	-	-
For all	25 (83.3)	30 (88.2)	24 (80.0)	31 (91.2)	27 (90.0)	34 (100.0)	0.366	0.248	0.782

Data are given as number of individuals n (%) within each sex and for the population as a whole.

V1=visit 1; V2=visit 2; V3=visit 3

¹For calculation of p-values Wilcoxon signed ranks test with pairwise exclusion was used.

4.1.2 Blood parameters

Untreated TC, untreated LDL and Lp(a)

The median value for the patients' first ever known untreated TC was 9.7 mmol/L and LDL was 5.9 mmol/L (table 3). These lipid values had been reduced to 5.2 mmol/L and 3.6 mmol/L respectively at V1, and was further reduced to TC 4.9 mmol/L and LDL 2.7 mmol/L after eight years of intensified treatment at V3 (table 4). The decrease was significant between all three visits.

The risk limit used in the clinic predicts an increased vascular diseases risk with a Lp(a) from 300 mg/L and over. In our population 26 (55.3 %) out of 47 patients with a measured Lp(a) are above this. The median Lp(a) was 346 mg/l.

Table 3. Untreated TC and LDL-c, and Lp(a) compared to risk limit

	V0		No > risk limit
	n	n	
Untreated TC	57	9.7 (6.0, 15.3)	57 (5.0 mmol/L)
Untreated LDL	47	5.9 (1.79, 11.2)	47 (3.0 mmol/L)
Lp(a)	47	346 (8, 2460)	26 (>300 mg/ml)

Data are presented as number of individuals n (%).

¹n indicates total number of total measured individuals.

V0=Visit 0; TC=total cholesterol; LDL=low density lipoprotein; Lp(a)=lipoprotein a.

LDL

The classical European recommendations for LDL targets have been LDL cholesterol lower than 2.5 mmol/L in primary and lower than 1.8 mmol/L in secondary prevention. The number of individuals who met their primary prevention treatment criterion of LDL below 2.5 mmol/L was markedly increased at V3 from 2 (3.1 %) to 15 (23.4%) (table 7). The number of individuals with a secondary prevention treatment target of LDL below 1.8 mmol/L, was 19 (29.7 %) patients at V3, and between V2 and V3 and V1 and V3 there was a significant improvement in the number of patients who met their treatment target ($p=0.012$ and $p=0.001$ respectively). The new American guidelines from December 2014 emphasizes much stronger than before the LDL treatment target of a 50 % achieved LDL-reduction. From V1 to V3 there was a significant increase in the number of participants who reached this ($p=0.033$), with a trend from V2 to V3 ($p=0.083$).

HDL

The HDL-C median value was 1.4 mmol/L for all three visits, and showed no significant differences. The non-HDL values on the other hand steadily decreased represented through a significant difference between V2 to V3 and V1 to V3 ($p=0.023$ and $p=0.002$ respectively).

Apo B, Apo A1 and Apo B/apo A1-ratio

The median APO B levels were 1.0 mmol/L for all three visits (table 6). The percentage of patients that had a apo B level <0.8 mmol/L at V3 were only 4.7 %, although another 18.8 % had an apo B value of exactly 0.80 mmol/L.

The median APO A1 medians were also quite stable on V1 and V2, although slightly increased on V3. This enhancement was significant between V2 and V3 and V1 and V3 ($p<0.001$ for both), maybe implying a possible decreased HDL particle size.

The median apo ratio was for women 0.62 at V1 and 0.61 at V3 respectively and for men at V1 0.73 and V3 0.67 respectively.

Fasting glucose, HbA1c and CRP

We found significant changes in both fasting glucose and HbA1c between V2 and V3 and V1 and V3 ($p<0.001$ for both), as the values have increased.

There were no significant changes in CRP at any of the visits. Further it keeps a low risk value below 1 mmol/L in median.

Table 4. Blood parameters at V1, V2 and V3.

	V1	V2	V3	p-value ¹ V1-V2	p-value V2-V3	p-value V1-V3			
TC	64	5.2 (3.5, 8.3)	64	5.2 (2.9, 9.5)	64	4.9 (3.3, 10.4)	0.230	0.063	0.015
HDL	64	1.4 (0.9,2.2)	64	1.4 (0.7,2.6)	64	1.4 (0.7, 2.3)	0.985	0.132	0.154
LDL	64	3.6 (2.2,6.2)	63	3.1 (1.6,7.3)	64	2.7 (1.7, 8.6)	0.021	0.013	0.000
TG	64	0.9 (0,2,3)	63	0.8 (0.3,4.2)	64	1.0 (0.5, 3.1)	0.570	0.002	0.008
Apo A1	64	1.4 (1.3-1.5)	64	1.4 (1.3-1.5)	64	1.6 (0.9-2.3)	0.268 ²	0.000	0.000
Apo B	64	1.0 (0.7,1.6)	62	1.0 (0.6,2.0)	63	1.0 (0.6, 2.3)	0.180	0.137	0.017
Apo ratio	64	0.69 (0.41, 1.22)	62	0.69 (0.3,2.0)	63	0.65 (0.36, 1.53)	0.018	0.014	0.183
Men	34	0.73 (0.41, 1.22)	32	0.71 (0.53, 2.0)	33	0.67 (0.36, 1.53)	-	-	-
Women	30	0.62 (0.41, 1.0)	30	0.63 (0.30, 1.17)	30	0.61 (0.36, 1.0)	-	-	-
Non-HDL	64	3.9 (2,3, 6.8)	64	3.7 (2.1, 8.4)	64	3.3 (1.9, 9.0)	0.149	0.023	0.002
Fasting glucose	58	5.0 (3.6,8.0)	60	5.0 (4.0,14.5)	64	5.2 (4.4, 14.3)	0.835	0.000	0.000
HbA1c	57	5.3 (4.9,6.8)	53	5.3 (4.8,10.6)	60	5.9 (5.0, 9.8)	0.350	0.000	0.000
CRP	60	0.7 (0.0,17.0)	60	0.0 (0.0,8.4)	64	0.6 (0.0, 6.1)	0.589	0.393	0.391

Data are given as mean (98 % confidence interval) or median (min, max).

¹Wilcoxon signed ranks test with pairwise exclusion was used to calculate p-values

²paired t-test was used for calculation of all p-values on this variable.

V1=visit 1; V2=visit 2; V3=visit 3; TC=total cholesterol; HDL=high density lipoprotein; TG=triglycerides; Apo A1=apolipoprotein A1; Apo B=apolipoprotein B; Apo ratio=apo B/apo A1-ratio; HbA1c=glycated hemoglobin; CRP=C-reactive protein.

Table 5. Number of subjects who met the treatment goals of LDL in V1, V2 and V3.

	V1		V2		V3		p-value ² V1-V2	p-value V2-V3	p-value V1-V3
	n ¹	n (%)	n	n (%)	n	n (%)			
LDL <2.5 mmol/L	44	2 (4.5)	40	4 (10.3)	40	15 (37.5)	-	-	-
LDL <1.8 mmol/L	20	0 (0.0)	24	1 (4.2)	24	0 (0.0)			
Change in no. reaching European treatment goal	-	-	-	-	-	-	0.257	0.012	0.001
LDL >50 % red	47	16 (25.0)	46	17 (26.6)	47	24 (37.5)	-	-	-
Change in no. reaching American treatment goal	-	-	-	-	-	-	0.414	0.083	0.033

Data are given/presented as number of individuals n (%).

¹n indicates total number of total measured individuals.

²Wilcoxon signed ranks test with pairwise exclusion was used to calculate p-values

4.1.3 Lifestyle

Diet

The Smart Diet Questionnaire was filled out by 58 (90.6 %) of the subjects at V1, and by 52 (81.3 %) at V2, and V3 by all the 64 subjects. The results on lifestyle are collectively shown in table 5a and 5b.

The Smart Diet score displayed significant improvement between both V1 and V2 ($p=0.047$) and V1 to V3 ($p=0.008$). This reflects an increase in total score at V2, which is further increased at V3.

The change in the Smart Diet total scores are also reflected in the Smart Diet categories, as there is a significant difference between V1 and V3 ($p=0.016$). There was an improvement, especially from medium to high category.

When comparing the patients' unedited Smart Diet score with the reviewed score resulting from the interview with the master student at the consultation, we find a significant increase in the master student evaluated Smart Diet score ($p=0.006$).

Further, when we evaluate the subgroups of the Smart Diet, there were also improvements in the patients' eating habits. The choices of dairy products was improved from V1 to V2

($p=0.042$), with a further trend towards improvement from V2 to V3 ($p=0.091$). This also applies to meat, where they already on V1 scored very high, but still further improved with a significant change from V1 to V2 ($p=0.042$). The choices of both dairy and meat products generally holds a high score on all three visits.

Interestingly, also the changes in fish and vegetable intakes showed improvements. There was a significant enhancement in fish intake between V1 and V3 ($p=0.039$). In the same manner there was a significant change in vegetable intake from V1 to V3 ($p=0.001$), and from V2 to V3 ($p=0.052$). This suggests that the biggest change happened between V2 and V3.

Regarding fruit intake, we do not find the same clear tendency as there were no significant differences between the visits. But, at V3 there were more individuals that ate three or more fruits daily, than at the other two visits.

Concerning the use of supplements, we found that the number of participants who use omega-3 or cod liver-oil was quite steadily around 60 % over the years. There was a reduction in the number who used one or more additional types of supplements.

Smoking

Of our 64 participants, 8 (12.5 %) were daily smokers at V3 (table 3b). Considering both current and earlier smokers the median years of smoking was 17 years at V3, with a median number of cigarettes per day of 12,5. There were no significant changes concerning smoking over this eight years period, however there seem to be a trend for a decrease in the number of party smokers and the more heavy smokers, in addition to there becoming fewer smokers in general. The participants, who are still smoking, are grouping in the category of smoking 6 to 11 cigarettes per day.

Alcohol

There were no significant changes concerning the alcohol intake (table3b). The pattern of frequency seems to be quite stable, although at V3 there were no longer any patients in the highest category corresponding to drinking 13 or more units of alcohol per week. 32.8 % of the patients drink less than 1 unit of alcohol per week, and 45.3 % drink 1 to 7 units per week. All the individuals in the category of drinking 8 to 14 units of alcohol per week were men

(data not shown). This means that at V3 all participants are low or moderate alcohol consumers. These numbers are patients' reported alcohol use.

Physical activity

We did not find any significant differences between the visits regarding neither physical activity nor intensity level of the physical activity performed (table 3b). But the patients reported quite good frequencies on physical activity already on V1. Now at V3, 27 (42.2 %) is physically active for more than 30 minutes on three or more occasions per week, and another 28 (43.8 %) on 1 to 2 occasions per week. Only 3 (4.7 %) report that they never do any work out. The type of activity performed was mainly of either moderate intensity, or a combination of moderate and high intensity. When separating the blood parameters on the frequency of physical activity we find gradients favoring the patients who are the most active. From never working out to more than three times per week we found the improvement of CRP from 0.7 to 0.0, LDL from 3.3 to 2.5, TG from 1.7 to 0.9, apo B from 1.3 to 0.9, HbA1c from 8.6 to 5.7, fasting glucose from 12.9 to 5.1, non HDL from 4.9 to 2.9, apo ratio from 0.93 to 0.61 (data not shown)

Table 6a. Lifestyle results of the subjects: Smart Diet at V1, V2 and V3.

Total n=64	V1		V2		V3		p-value ² V1-V2	p-value V2-V3	p-value V1-V3
	n ¹		n		n				
SD score patient	58	35.3 (26, 43)	52	37.0 (28, 42.5)	64	37.25 (26, 43.5)	0.047	0.494	0.008
SD score consultation	-	-	-	-	64	37.3 (0.006)	-	-	-
SD category (%)	60	93.8	52	81.3	64	100	0.180	0.433	0.016
1 (< 30)	4	6.3	2	3.1	3	4.7	-	-	-
2 (30-37)	39	60.9	29	45.3	30	46.9	-	-	-
3 (> 37)	17	26.6	21	32.8	31	48.4	-	-	-
SD subgroups									
<i>Dairy (1-12)</i>	58	10 (8, 12)	55	11 (8, 12)	65	10.5(6, 12)	0.012	0.091	0.173
<i>Meat (1-6)</i>	58	6 (3, 6)	58	6 (4, 6)	65	6 (3,6)	0.042	0.535	0.387
<i>Fish (1-6)</i>	57	4 (2,6)	58	4 (2,6)	65	4 (2,6)	0.364	0.123	0.039
<i>Vegetables</i>	57	89.1	57	89.1	64	100	0.255	0.052	0.001
1 (<1)	27	42.2	24	37.5	17	26.6	-	-	-
2 (1-2)	23	35.9	24	37.5	30	46.9	-	-	-
3 (>=3)	7	10.9	9	14.1	17	26.6	-	-	-
<i>Fruit</i>	57	89.1	56	87.5	64	100	0.422	0.527	0.881
1 (<1)	18	28.1	20	31.3	22	34.4	-	-	-
2 (1-2)	25	39.1	22	34.4	26	40.7	-	-	-
3 (>=3)	14	21.9	14	21.9	16	25.0	-	-	-
Supplements	59	92.2	56	87.5	64	100	-	-	-
None	18	28.1	12	18.8	22	34.4	-	-	-
Cod-liver oil	18	28.1	19	29.7	18	28.1	-	-	-
ω-3 capsules	24	37.5	23	35.9	19	29.7	-	-	-
Multivitamine	11	17.2	11	17.2	8	12.5	-	-	-
Other	11	17.2	11	17.2	10	15.6	-	-	-

Data are given/presented as mean (95 % confidence interval), median (max, min) or number of individuals n (%).

¹n indicates total number of total measured individuals.

V1=visit 1; V2=visit 2; V3=visit 3; SD=Smart Diet

²Wilcoxon signed ranks test with pairwise exclusion was used to calculate p-values

³p-value for the difference between the patients' own SD-score compared to the SD-score resulting from the interview.

Table 6b. Lifestyle results: Smoking, alcohol and physical activity at V1, V2 and V3.

Total n=65	V1		V2		V3		p-value ² V1-V2	p-value V2-V3	p-value V1-V3
	n ¹		n		n				
Smoking (%)	63	98.4	59	92.2	64	100	0.809	0.664	0.526
0 (no)	48	75.0	47	73.4	53	82.8	-	-	-
1 (<=5)	4	6.3	1	1.6	1	1.6	-	-	-
2 (6-10)	2	3.1	4	6.3	6	9.4	-	-	-
3 (>=11)	3	4.7	2	3.1	1	1.6	-	-	-
6 (Party smoker)	5	7.8	5	7.8	3	4.7	-	-	-
7 (yes)	1	1.6	0	0.0	0	0.0	-	-	-
Earlier smoker (yrs)	-	-	-	-	17	17 (1, 45)	-	-	-
Earlier smoker (No. sig/day)	-	-	-	-	17	12.5 (1, 40)	-	-	-
Alcohol consumption	59	92.2	58	90.6	64	100	0.157	0.394	0.827
0 (Nei)	11	17.2	8	12.5	9	14.1	-	-	-
1 (<1)	17	26.6	15	23.4	21	32.8	-	-	-
2 (1-7)	28	43.8	29	45.3	39	45.3	-	-	-
3 (8-14)	1	1.6	5	7.8	5	7.8	-	-	-
4 >15	2	3.1	1	1.6	0	0.0	-	-	-
Physical activity >30 min	60	93.8	58	90.6	64	100	0.828	0.776	0.985
never	-	-	-	-	3	4.7	-	-	-
1 (<1/uke)	11	17.2	11	17.2	6	9.4	-	-	-
2 (1-2)	25	39.1	21	32.8	28	43.8	-	-	-
3 (>=3)	24	37.5	26	40.6	27	42.2	-	-	-
Intensity of the physical activity	5	7.8	40	63.1	58	90.6	0.317	0.329	0.317
1 (High intensity)	-	-	-	-	6	9.4	-	-	-
2 (Moderate)	2	3.1	19	29.7	26	40.6	-	-	-
3 (Mixed)	3	4.7	21	32.8	26	40.6	-	-	-

Data are given/presented as mean (95 % confidence interval), median (max, min) or number of individuals n (%).

¹n indicates total number of total measured individuals.

V1=visit 1; V2=visit 2; V3=visit 3; SD=Smart Diet

²Wilcoxon signed ranks test with pairwise exclusion was used to calculate p-values

4.1.4 The patients preferences

The Patients' Preferences questionnaire was only collected at V1 and V3. During these eight years we observe a small shift in the perception of "whether lifestyle is equally as important as medication", towards that these two are considered to be equally important, though this change was not significant (table 4). The main part of the population has always fully or partly agreed in this statement.

Further, there might also be a small, non-significant shift in the number of patients who "wish their cholesterol level to be as low as possible". Approximately 10 % moves from "fully agree" to "partly agree" from V1 to V3, but still the main part of the population has always fully agreed or partly agreed that they wished their cholesterol level to be as low as possible.

From the preference questionnaire there was one particular question that showed a significant change from V1 to V3. This was whether the patients "preferred to have little side effects rather than low cholesterol values". A large proportion of the patients have shifted from a fully disagreement to this statement to a neither/nor or partly agreement ($p=0.003$), which means that patients now express an higher preference for not having side effects even through the cholesterol level will be higher.

Table 7. Results from the patients' preference questionnaire at V1 and V2.

Total n=65	V1		V3		P-value ² V1-V3
	n ¹		n		
Lifestyle is as important as medicines	63	98,4	64	100,0	0.110
Fully agrees	36	56,3	39	60,9	-
Partly agrees	18	28,1	23	35,9	-
Neither nor	4	6,3	1	1,6	-
Partly disagrees	5	7,8	1	1,6	-
Fully disagrees	-	-	-	-	-
Wants as low cholesterol as possible	63	98,4	64	100,0	0.310
Fully agrees	51	79,7	45	70,3	-
Partly agrees	10	15,6	17	26,6	-
Neither nor	1	1,6	-	-	-
Partly disagrees	-	-	1	1,6	-
Fully disagrees	1	1,6	1	1,6	-
Wants little side effects before low cholesterol	63	98,4	64	100,0	0.003
Fully agrees	3	4,7	5	7,8	-
Partly agrees	8	12,5	14	21,9	-
Neither nor	14	21,9	21	32,8	-
Partly disagrees	20	31,3	20	31,3	-
Fully disagrees	18	28,1	4	6,3	-

Data are given as number of individuals n (%).

¹n indicates total number of total measured individuals.

²Wilcoxon signed ranks test with pairwise exclusion was used to calculate p-values

4.2 CVD vs non-CVD

4.2.1 Characteristics

All data are from V3.

The CVD group consisted of 14 (70 %) men, and the median age was as eight years higher than for the non CVD group (table 8). The difference in age was found to be significant ($p=0.005$), but not the gender distribution. A bigger fraction of the CVD group was treated for hypertension; 15 (75 %) compared to 6 (13.6 %) in the non-affected group. The median of systolic blood pressure was below 140 mmHg in both groups, although the CVD group was

very close to it. Both these differences were significant ($p<0.001$ and $p=0.013$ respectively). The diastolic blood pressure was on the other hand not significantly different. In the CVD group 3 (15 %) was treated for diabetes mellitus, compared to 3 (6.8 %) in the non-CVD group –a non-significant difference.

There was a significant 7.7 cm difference ($p=0.030$) in the waist circumference between the two groups, CVD being the highest, and also a slightly non-significantly higher BMI and weight in the same group. A bigger fraction of CVD patients desired to reduce weight 15 (78.9 %) against 24 (57.1 %) in the non-CVD group (data not shown).

All except one participant in each group were on statin therapy. Rosuvastatin was the main statin, being used by 19 (94.7%) and 28 (63.6 %), with atorvastatin as number two. The non CVD group also had 2 (4.5 %) patients on Simvastatin. Out of the 19 statin users in the CVD group, all were receiving high intensity treatment, compared to 35 (81.4 %) of the patients with no documented CVD. The remaining 8 were receiving medium intensity statin treatment. There are also a higher percentage of CVD patients receiving both ezetimibe and cholesevelam. Only one patient in the CVD group was also taking niacin. None of these results was significantly different, but there was a trend for a higher part of the CVD group taking cholesevelam ($p=0.082$).

There were a higher percentage of CVD patients who had certain, probable and possible side effects than in the non-CVD group. There were not any of the CVD patients who had “treatment target reached” as their reason for not intensify their medical treatment. They also constituted a bigger part of the categories of “did not wish to increase the medication”, who had “side effects” as a reason to not increase, that “the doctor say no”, or that they “already were on maximal treatment”.

Table 8a. Characterization of individuals with CVD vs no CVD at V3.

Total n=64	CVD		No CVD		p-value ²
	n ¹		n		
Characteristics					
Age	20	58 (45, 74)	44	50 (27, 76)	0.005
male/female	20	14/6	44	21/23	0.100
Comorbidity					-
Hypertension	15	75	6	13.6	0.000
Diabetes	3	15	3	6.8	0.302
Clinical measurements					-
Waist circumference	19	97.7 (76, 142)	40	90.0 (65, 140)	0.030
BMI	20	26.7 (20.8, 41.1)	44	25.1 (18.3, 42.1)	0.524
BP Systolic	16	138.5 (114, 165)	37	126 (105, 164)	0.013
BP diastolic	16	75 (67, 101)	37	76 (43, 96)	0.992
Statins	-	-	-	-	0.303
Rosuvastatin	18	-	28	-	-
Atorvastatin	1	-	13	-	-
Simvastatin	0	-	2	-	-
Statin Intensity	-	-	-	-	0.901
High intensity	19	95.0	35	79.5	-
Medium intensity	0	0	8	18.2	-
Low intensity	0	0	0	0	-
Non compliant last month	1	5.0	1	2.3	-
Ezetimibe	17	85	34	77.3	0.904
No on maximum dose	17	85	34	77.3	-
Inegy	0	0	1	2.3	-
Non compliant last month	0/3?	0	0/9?	0	-
Cholestagel	10	50	9	20.5	0.082
No on maximum dose	7	35	6	13.6	-
mean dose mg/day	-	3750	-	3750,00	-
Niacin	1	5.0	0	0,00	0.147
Side effects (certain and probable/possible)	7/3	35/15	11/3	25/6.8	

Data are given/presented as mean (95 % confidence interval), median (min, max) or number of individuals n (%).

¹n indicates total number of total measured individuals.

BMI=body mass index; BP=blood pressure

High intensity statin therapy is defined as atorvastatin 40-80 mg or Rosuvastatin 20-40 mg. Moderate intensity statin therapy is defined as Atorvastatin 10-20 mg, Rosuvastatin 5-10, Simvastatin 20-40 mg, Pravastatin40-80 mg, Lovastatin 40 mg, Fluvastatin 40 mg or Pitavastatin 2-4 mg

²Mann WhitneyU test was used to calculate p-values.

4.2.2 Blood parameters

The CVD group had a higher untreated TC median, and a slightly higher treated TC than the non CVD group. They also had a slightly lower HDL, and a higher TG, apoB, apo ratio, fasting glucose and HbA1c. The untreated LDL was actually higher in the non-CVD group with a median value of 6.6 mmol/L compared to 5.0 mmol/L in the CVD group. The untreated lipid values are mostly reported from private doctors, and are insecure data not always taken in a fasting state. Further, the CVD group had also a median Lp(a) of 657 versus 278 among the non-CVD patients, thus a median above the reference area, whereas the non-CVD patients have not.

4.2.3 Lifestyle

Table 8 shows all lifestyle variables on CVD patients and non CVD patients. There is a non-significant higher percentage of the CVD patients that are current smokers. Combining these with former smokers, they have as a group a significantly longer exposure time to smoking than the non CVD group ($p=0.044$), with 21 versus 6 years for the non CVD patients.

The non CVD group scored slightly better though not significantly higher on the Smart Diet questionnaire total score, with no bigger difference in Smart Diet categories. They also ate slightly more fruit and vegetables (data not shown). The CVD group made slightly better choices concerning dairy products, but the two groups scored equally well on the meat and fish subcategories. A higher percentage in the CVD group is taking cod liver oil or omega 3 capsule supplements.

When considering the level of physical activity, there was a higher percentage of the CVD group that works out three times or more per week. We also found that they more often hold a moderate intensity of their work out than the non-CVD patients (data not shown). This was not a significant difference.

We did not find any particular differences in alcohol consumption between the groups.

Table 8b. Blood parameters and lifestyle differences for CVD vs no CVD at V3.

Total n=64	CVD		Non-CVD		p-value ²
	n ¹	-	n	-	-
Blood Lipids	20	-	44	-	-
Untreated TC	16	10.6 (6, 15.3)	41	9.1 (6.5, 13.5)	0.120
Untreated LDL	17	5.0 (1.8, 8.5)	30	6.6 (3.1, 11.2)	
TC	20	4.85 (3.3, 6.5)	44	4.85 (3.3, 10.4)	0.851
LDL	20	2.9 (1.8, 5.2)	44	2.7 (1.7, 8.6)	0.881
HDL	20	1.3 (0.7, 2.3)	44	1.4 (0.9, 2.3)	0.716
TG	20	1.3 (0.6, 2.3)	44	1.0 (0.5, 3.1)	0.144
Lp(a)	16	657	31	278	0.055
ApoB	19	1.1 (0.8, 1.7)	44	0.9 (0.6, 2.3)	0.080
ApoA1	19	1.6 (0.9, 2.3)	44	1.6 (1.1, 2.3)	0.568
Aporatio	19	0.69 (0.43, 1.42)	44	0.63 (0.36, 1.53)	0.413
Non-HDL	20	3.30 (2.20, 5.50)	44	3.25 (1.9, 9.0)	0.638
Other blood parameters					-
CRP	20	0.68 (0.00, 3.3)	44	0.00 (0.00, 6.10)	0.352
Glucose	20	5.7 (4.7, 14.3)	44	5.1 (4.4, 8.5)	0.008
HbA1c	19	6.1 (5.6, 9.8)	41	5.8 (5.0, 7.4)	0.003
Lifestyle					
<i>Active smoker</i>	4	20	7	15.9	0.700
<i>No of years of smoking</i>	13	21 (1, 45)	14	6 (1, 22)	0.044
SmartDiet					-
<i>Totalscore</i>	20	37 (28, 41)	44	37.5 (26, 43.5)	0.509
Smart Diet categories					0.719
<i>Low</i>	1	5	2	4.5	-
<i>Medium</i>	10	50	20	45.5	-
<i>High</i>	9	45	22	50	-
cod liver oil or omega 3 capsules	13	72.2	24	55.9	-
Trening/mosjon					0.776
<i>never</i>	2	10	1	2.3	-
<i><1 per week</i>	2	10	4	9.1	-
<i>1-2 times per week</i>	6	30	22	50	-
<i>>=3 times per week</i>	10	50	17	38.6	-
Alcohol					0.686
<i>never</i>	4	20	5	11.4	-
<i><1 per week</i>	6	30	15	34.1	-
<i>1-7 times per week</i>	8	40	21	47.7	-
<i>8-14 times per week</i>	2	10	3	6.8	-

Data are given/presented as mean (95 % confidence interval), median (min, max) or number of individuals n (%).

¹n indicates total number of total measured individuals.

BMI=body mass index; BP=blood pressure

High intensity statin therapy is defined as atorvastatin 40-80 mg or Rosuvastatin 20-40 mg. Moderate intensity statin therapy is defined as Atorvastatin 10-20 mg, Rosuvastatin 5-10, Simvastatin 20-40 mg, Pravastatin40-80 mg, Lovastatin 40 mg,

Fluvastatin 40 mg or Pitavastatin 2-4 mg

²Mann WhitneyU test was used to calculate p-values.

5 Discussion

5.1 Subjects and method

The Lipid clinic at Rikshospitalet, Oslo University Hospital (OUS), has been the central institution for treatment of patients with FH in Norway for 30 years. The clinic has a unique patient population of FH in a northern-European context, and has a long research tradition concerning FH. This gives an opportunity for clinical evaluation of the treatment for these patients. Many of the patients, and even whole families, have participated in clinical studies over the years. They are therefore often well aware of the importance of doing such clinical studies, and the progress in medical knowledge this entails. Furthermore, many patients also have experienced CVD events in close family, and they carry the insight of their 50 % chance that the following generations will inherit the disease, so they are often a highly motivated and compliant group.

During the recruitment process of participants to this kind of quality of real treatment study there is a considerably risk of having a selection bias. There probably might be a difference between the patients who wants to participate and those who do not. The patients who are the most interested to continue participating on all three visits through these eight years, might also be the same patients who are the most compliant to treatment recommendations. Some cohort studies have shown this tendency, especially an overrepresentation of high educated individuals, a group known to lead a healthier lifestyle than the general population (108) (oslo undersøkelsen). This will possibly lead to an overestimation of the compliance to the treatment, when transferring the results to the general population of FH patients treated at the Lipid clinic.

In our study all adult patients scheduled for consultation from the 9th of January 2006 to the 9th of July 2006 was invited to participate on V1. On V2 and V3 there has been a marked drop out (figure x) that might lead to a further selection bias for the remaining population.

However, according to our comparison of the 64 patients in our sample at V3 to the 426 patients in the starting population of V1, we find a similar median age of 45 to 43 years respectively. In the same manner we found the populations to consist of 54.7 % and 52.1 %

men and 45.3 % and 47.9 % women on V3 and V1 respectively. Still we cannot rule out that the excerpt sample of this thesis might differ from the whole FH patient population in other aspects.

The patient population covers a large age span, and there is a wide difference between patients in how long they have been treated at the Lipid clinic. Some of the patients have received an early diagnosis, and have grown up in a home with treatment compliant parents. Hence, they might have followed the lifestyle recommendations their whole life, in addition to starting their medical treatment very early. This is in sharp contrast to patients who discover their FH mutation due to for example a CVD event as an adult, and having for many years been exposed to untreated LDL-c and a traditional northern European unfavourable diet. As CVD is a disease that develops over many years, this difference might have a large impact on the relative risk, but this aspect has not been accounted for in this study.

The time span of the study makes it possible to analyse the relation between different variables and end points such as death and CVD events. But, the excerpt sample of 64 patients is such a low number that this will weaken the strength of the results. It is planned to complete V3 including all participants from V2 (n=332), that will markedly increase the n, and strengthen the statistical power of the later results (109).

TTTFH is a prospective cohort study on FH patients carried out in the ordinary treatment routine in the Lipid clinic. The collected data are describing the present state at the visits, and summarises retrospectively for certain variables what has happened with the patients before and between the visits. The lifestyle data are obtained before the encounter of a potential end point. In this way recall bias are avoided. However, the study population consists of both patients who are receiving primary and secondary medical treatment. Among the patients which have already experienced a CVD event prior to V1 or after, we cannot rule out that this might in some way affect their registrations.

The patients, who have been treated at the Lipid clinic for many years, are well aware of the treatment provider's anticipations and recommendations. This will potentially introduce a pleasing or reporter bias, consciously or unconsciously. The dietary and lifestyle data represents the weakest data in this context. Generally the patients might underreport the use of variables considered negative in relation to FH, like saturated fat and sugar holding foods,

alcohol and smoking, while they might overreport variables positively associated to FH like fruit, vegetables and fish intake, as well as the level of exercise (109, 110).

Information bias occurs if the collection of variables is not standardized, but is collected differently for different patients. In this study the patients had to fill out the Smart Diet and patient's preferences questionnaires on their own in advance of the consultation at each visit, hence the interview was conducted afterwards. The remaining variables have been collected by the doctors in the Lipid clinic that have followed the Doctor's scheme during the consultation, and in this way have asked the same questions every time. Since this study was conducted as a part of the ordinary clinical routine, there will be a variation in the execution between the different doctors as well as other health personnel on the different visits, which implies a certain information bias. Each patient has in general been relegated to the same doctors on V1 and V2. On V3 all the doctor's consultations were conducted by the same doctor. This is the same doctor that also met the largest number of patients on V1 and V2. Hence a large number of patients have been to the same doctor at all three visits, reducing the variation in the methodology within each patient. We cannot on the other hand rule out that there is a difference between the various doctors, giving a base for information bias even though they have all worked by the same protocol.

Weight and height have mostly been collected at the Lipid clinic using the same equipment, but this slight variation in collection of anthropometric variables is a weakness in our dataset. On V3 all anthropometric data was collected by the clinical nutrition master student.

When calculating the BMI the measured height at V3 was used for all three visits. Height measurements were missing for several individuals on V2, and at V1 some height measurements were self-reported or measured by different personnel. Some of the self-reported heights might even be older than the time span of the study, as many reported the number of centimeters measured when serving military at an age of eighteen to nineteen years. We therefore concluded that there would be less impact from the possible decrease in height during these eight years, than the potential systematic biases the two first visits would introduce.

When working with humans in studies, there will always be a possibility for certain unforeseen circumstances that will affect the procedures, for instance as in the use of the Smart Diet Questionnaire. Due to difference in perceptions of the meaning of words and

concepts between individuals, in addition to subjective ideas of frequencies, questionnaires might be less precise in describing certain variables than the ruling golden standard in a particular area (111). Although the Smart Diet is of great benefit in the outpatient clinic, it has been shown to have certain limitations in a research context. As earlier studies have not been able to find a correlation between higher Smart Diet score and cholesterol levels, this might imply a low sensitivity in the questionnaire. The lack of discrepancy in how much the different questions contributes to the total score and certain lack of quantification might be the reason to this (112).

Some of the patients have met a clinical dietician at V1 and V2, which usually entails a change in the Smart Diet score compared to the patient's own score, an also to the score summarised and reported by the doctors. This is further discussed in the section on the Smart Diet results. This randomness is also found on V3, as a few patients (n=9) did not fill out the Smart Diet in advance of the interview, which then has been filled out together with the master student.

The lack of control group in this study opens for the possibility that the results have been affected by other factors than the treatment at the Lipid clinic.

When comparing the patients who have developed CVD with those who have not,

Data processing

On V3 the doctor and master student have gone through and controlled all data from all three visits. This was conducted in a manner were only one person plotted all the data of the same variable. This strengthens our dataset as it rules out inter-individual variability in data processing within the same variables. The controlling measures taken before and during data processing, also contribute to prohibit errors, and further strengthen the data. Despite this, we cannot rule out the possibility of errors not being discovered, or that the patients intentionally or unintentionally have given erroneous information.

Statistics

Some variables were normal distributed, and therefore analysed with parametric statistics, The main part of our variables was skewed and thus analysed with non-parametric statistics. The skewed data may often have been a result of the small sample size, and therefore we will

discuss the possibility that some p-values in the proximity to significance might become statistically significant in a bigger sample. The upper limit for this was set to $p<0.100$ or a striking difference in percentage between the compared variables.

The differences and development in all variables from V1 to V2, and V2 to V3 were of our main interest in addition to a descriptive look at potential differences between patients who develop CVD versus patients those who do not. We mainly calculated frequencies, cross tabulations and exploration analyses. Correlation and regression analysis to explore the different variables' influence on risk is also of great interest, although not explored here.

Two of the included subjects are due to non-compliance and fear of side-effects not on medication at V3. As this represent a normal variation within their treatment state, they are still included by the same criteria as for the other two visits.

We have not collected data on diabetes status at V1 and V2. Those who were treated for diabetes at V3, was therefore set to the treatment target of 1.8 mmol/l at V1 and V2, as well. Age at medical treatment start has not been estimated in this thesis, since that has not been actively used in the clinic

5.2 Results

5.2.1 Characteristics

Our selection of 64 participants is of similar age and share the same relatively balanced gender distribution as the bigger population of patients. This means that our sample might be representable for the larger group, potentially implying at least some transferability.

The participants have held a stable weight with increasing age throughout the visits over eight years, in contrast to the general population who gain weight as they get older (113). This consistency is also reflected in the stable BMI and waist circumference, although this is above what is recommended by the International Diabetes Federation for both for men and women separate (57). Even though they have significantly lowered their BMI, V3 shows a median BMI representing a slightly overweight population. However, a BMI characterized as overweight has been shown to have a significantly lower all-cause mortality (114). On this visit 3.4 % of the women were underweight, 48.3 % women and 31.4 % men had a normal

BMI, 27.6 % women and 40 % men were overweight and 20.7 % women and 28.6 % men were obese. As there is no recent weight data on the Norwegian population as a whole, and the weight is reportedly increasing in Europe, we have instead made a comparison to the yearly report from the Swedish institute of public health. The inhabitants in our neighbour country might be considered to be quite similar to Norwegians concerning habits and lifestyle. They have reported that 54 % of all women and 43 % of all men had normal weight, 29 % women and 42 % men were overweight and 14 % of both genders were obese in 2013 (115). Thus, in our study group there was a slightly lower fraction that had a normal weight or were overweight than in the Swedish general population, but rather a higher percentage that were obese. This indicates that the baseline weight in the FH population at V1 might have been even higher compared to the general population, than it was at V3.

A high percentage of the participants expressed a desire to reduce their weight, with no differences between the sexes. In the general Norwegian population there is a predominance of women over men who desire a reduction in weight. Our results may show an increased understanding of the traditional negative consequences of overweight and obesity as seen associated with the abdominal type obesity.

At V3 6 (9.4 %) of our patients was taking medication for DM. In Norway, there was in 2012 125 000 people registered for a prescription on DM medications, corresponding to approximately 2 % of the whole population. The percentage might be a little higher as the whole population was used for calculation, and not only adults. This might imply that there is a higher fraction of our study population that have DM, than in the general population. However, there is a possibility that a considerably larger part of our study population have discovered their DM than in the general population due to the more frequent blood measurings, as the number of undiagnosed DM is estimated to at least be of equal size as that of diagnosed DM. In a global context the WHO has estimated the percentage of adult individuals with DM in 2014 to be approximately 9 %, although a large fraction of this probably are in low- and middle-income countries (72).

The intensity of the lipid medication is a compromise between three factors; the need for molar LDL reduction, the patients' perceived side effects of medication and their attitudes towards medical treatment.

Nearly 85 % of our patients were on high intensity statin therapy. In addition there was slightly more than 50 % who use a second lipid medication, almost always ezetimibe. One third of the patients needed triple lipid medication. Despite of this, on V3 only one third actually reached the LDL treatment target. Almost 40 % reached the milder treatment target of 50% LDL reduction

There might be as many as 24 (37.5 %) of the patients who experience side effects from their medication. This probably reflects both the intensity of the medication, as well as quite a high acceptance for side effects among the FH patients. The patients' preference scheme unravels a high desire among the patients for their cholesterol level "to be as low as possible", and that this was weighted heavier than "to have no side effects" by approximately 60 % of the participants on V1. This has significantly changed over the eight years, and on V3 there were less than approximately 40 % who agreed to that. This may indicate that the struggle from living with side effects for many years, is affecting the patients. And, together with the knowledge of the highly improved prognosis of CVD, they take a more relaxed attitude towards their disease, somewhat compensating with an improved lifestyle.

We have not collected data on xantomata, for persentation in this paper.

5.2.2 Blood parameters

The lipid values have generally improved during the eight years of the TTTFH study. TC, LDL, apo-ratio and non-HDL are all significantly decreased, suggesting a decrease in the patients' CVD risk.

The American guidelines from AHA/ASC 2013 have especially emphasized the treatment target of a 50 % reduction in LDL. In our study group this was accomplished increasingly from V1 to V2. The proportion of patients reaching this treatment target significantly rose from 16 (25 %) on V1 to 24 (37.5 %) of the whole group at V3. Due to the high baseline LDL values, patients who met the 50 % reduction most often still did not meet the ESC/EAS guidelines in 2006 with a LDL treatment target of < 2.5 mmol/l in primary prevention and < 1.8 mmol/l in secondary prevention or the presence of diabetes mellitus. Among our patients with a < 2.5 mmol/l treatment target, there has been a significant rise in the number achieving this during the study, starting at only 2 (4.5 %) with success in 2006, rising to 15 (37.5 %) in 2014. Still, none of the patients in our sample with the treatment target of LDL < 1.8 mmol/l,

managed to reach this at V3. A total of 15 (23.4 %) of the whole study population reached the treatment target of below 2,5 mmol/l. Although this is a rather low fraction, other studies have found similar results, both internationally (116, 117) and at the Lipid clinic (Master thesis of Ida Halvorsen). In these reports the main reason was concluded to be both an acceptance of higher LDL cholesterol than the recommended among the doctors, in combination with the high baseline LDL cholesterol of the FH-patients. Still there has been a clear improvement in our group from V1 to V3 concerning this. LDL was the only blood parameter with a significant change between all three visits, and shows a total decrease of 0.9 mmol/l from V1 to V3. As a reduction of 1.0 mmol/l in LDL cholesterol leads to a 20 % lowering in risk of mortality from CVD events, this decrease might be of health benefit to the patients.

Although the median of apo B is the same at all three visits, it has significantly increased between V1 and V3. Seen in context with the decrease in LDL, this is unexpected. As the TG was below 4.52 mmol/l we used the Friedewald formula to calculate LDL, as a control to the direct measurement of LDL, based on the medians of TC, HDL and TG. This gives a LDL level of 3.40, 3.44 and 3.05 mmol/l on V1, V2 and V3 respectively. Using the measured value of each person gave a median LDL of 3.46, 3.19 and 2.73 mmol/l on V1, V2 and V3 respectively, maybe demonstrating the influence the use of medians might have on the data.

The difference between LDL and apo B might be due to a slight switch towards smaller LDL particles. But it may also be due to the small sample size in the study.

HDL and CRP are the only blood parameters with no significant changes over the years. One major influence on HDL is physical activity, and as we did not find significant changes there either, this may explain some of the reason. Abdominal adiposity, did not either change so much over the years, that it could have reduced HDL. Statins, ezetimibe and niacin have also been shown to increase the HDL level. All of the patients started, at least their statin therapy ahead of V1, so most of this effect might already have been established before the start of the TTTFH study. FH patients may have lower levels of HDL than the general population (118), but our in our sample the patients were within the normal range for both sexes. TG levels are normally the same for FH patients as in the general population. The TG levels are elevated in FH by the same reasons as in the normal population.

The level of TG in our sample has slightly increased over the years together with fasting glucose and HbA1c. But the TG is still below the recommended 1.7 mmol/l. TG elevation is

often seen in association with the metabolic syndrome together with an increase in the HbA1c and fasting glucose. The reported slight increase in both glucose and HbA1c reflect a worsening in the glucose metabolism.

In our study group, 5 and 19 more other than the six participants who were treated for diabetes had a fasting glucose and HbA1c above 6mmol/l and % respectively. The median value is still within the reference area. Some publications have stated that an HbA1c in the area between 6.0 and 6.5 % give an increased risk of developing diabetes.

If the LDL particles are smaller, the increase in blood glucose is a bad combination due to the longer time each LDL particle have spent in the circulation and vessel walls, enhancing the interaction time. High blood glucose leads to more glycation of the hemoglobin, giving a high HbA1c. This will also give more glycation of the LDL particles in the same manner, further contributing to the evolution of atherosclerotic plaque. One might expect a small, natural elevation in HbA1c from V1 to V3, as studies have shown a correlation between HbA1c and age in individuals with normal glucose tolerance (119-121). The HbA1c median in our study population increased from 5.3 to 5.9 %, and this represents a higher increase than the nearly 0.1 % increase expected from ageing, hence indicating that other factors are contributing as well, like metabolically active visceral fat and an energy excess. But, we have to notify, this worsening of HbA1c can also have been influenced by the diabetogenic potential of the statins (122).

The CRP median is below 3, with seven participants having a value between 3 and 6.1 that might indicate a moderately increased CVD risk, but can very well be the initiation or rest of an immune response towards something else than the atherosclerotic process in the vessel wall.

Lp(a) is an independent risk factor of CVD, and shows a proportional elevation in risk with increasing Lp(a) levels. The Lp(a) median in our study population is above the risk limit, indicating that more than 50 % is above the risk limit, and even more if you set the risk limit as low as recommended by Nordestgaard et al. (40).

5.2.3 The Smart Diet

Lifestyle factors may vary with different seasons of the year. The fall and early winter season in which the visit V3 was carried out, might therefore affect the results.

Comparing the patient's unedited Smart Diet score with the reviewed score resulting from the interview at the visit, show that when the patient and, the master student critically re-examine the Smart Diet together, the result is a significant higher score. This might be due to pleasing bias, clearing up misunderstandings of the questions, or that the patient through discussion has a realization of their real eating habits, for instance such as that the patient actually eats vegetables on the sandwich as well, and not only for dinner. This change in total score might be occurring in the ordinary consultations at the Lipid clinic as well.

As some of the total scores from visit 1 and 2 are from a consultation with a clinical dietitian or a doctor, and others are not, this will imply that there exists certain information bias in these data. Although, as some patients had not filled out the Smart Diet in advance of the interview on V3, a few scores might also be biased in this way, thus applying this to all three visits.

Taking all this into account, we choose to interpret the steady increase in Smart Diet score as an improvement in the patients' eating habits. They are becoming over the years somewhat more skilled in making conscious choices, and to further implement the recommendations into their everyday diet. Of course, the significant increase in Smart Diet score might also be a matter of whether the patient to a higher degree has learned what we want them to eat, and lets this affect how they fill out the questionnaire during the years as a patient at the lipid clinic, compared to 2006. Although, since the subjects have been patients at the Lipid clinic for several years in advance to V1, the roughest pleasing bias and misunderstandings should already be established and solved prior to this, and thus affect the scores collected in this study to a smaller degree.

When having a closer look at the subgroups of the Smart Diet, we might see an interesting pattern. There is? a significant enhancement in the dairy, meat, fish and vegetable questions /answers?. While the significant change in the choices made concerning dairy products and meat products was seen already between V1 and V2, the change in fish and vegetable intake are seen with a delay compared to this. Between V1 and V3 there was a significant change in the frequency of vegetable consumption, and a trend for change between V2 and V3. This

might imply that ordinary dairy and meat products were already everyday foods in their diet at V1, and have been easy to switch to low fat products later. To increase the frequency in intake of fish and vegetables on the other hand, will often be a bigger intervention in a person's habit, hence taking longer time to implement...

In Norway approximately 15-20 % takes cod liver oil or omega 3 supplement three or more times per week. Unfortunately we do not have frequency estimation on our data. It might not be unreasonable to assume that it is a daily intake also for most of the 57.8 % of the participants.

At V3 all participants are low or moderate alcohol consumers. Åkesson et al have recently shown this to be low risk behaviour. High alcohol consumption is considered an unhealthy habit. The Global Burden of Disease Project lists alcohol consumption as risk factor number eight for death in the world, and the fourth risk factor for the burden of non-communicable diseases . To be a healthy habit the alcohol consumption has to be below 10-30 gram alcohol daily.

At V3 12.5 % were daily smokers with no difference between the genders. This is the same as in the general population in Norway, where approximately 13 % of all men and women smoke. We also find the same trend in our sample as in the society; a higher mean age among daily smokers than for the non-smokers and party smokers (123). A smaller proportion of our study population is party smokers at V3; only 4.7 % compared to approximately 9 % in the general Norwegian population. There is a decline in the number of smokers in Norway, as well as a shift in the general opinion against smoking. This, in combination with a persistent argument against smoking during consultations at the Lipid clinic will contribute to a further decrease in smokers in the FH population

The WHO has stated that there is an inverse association between physical activity and the risk of CVD. The national recommendations concerning physical activity recommend at least 150 minutes of moderate intensity per week or a minimum of 75 minutes of high intensity per week, or a combination of these two () .

The general population is becoming heavier and slightly less physical active with increasing age. Increased body weight is well known to influence on the lipid profile in the population. Three health surveys in Nord-Trøndelag performed in 1984-86, 1995-97 and 2006-08 have

shown that on average, men have increased their BMI by 2.2 kg/m^2 and women by 1.8 kg/m^2 over a period of 22 years (113). The annual weight gain during the period was 0.28 kg for men and 0.24 kg for women. Levekårsundersøkelsen found in 2007 that 42 % of the Norwegian population in the age of 16 to 79 was physically active three times or more, with an ongoing gradual increase, although not significant (124). In our population 42.2 % is physically active for more than 30 minutes three times or more per week at V3, with another 43.8 % 1-2 times per week. Our study population has a steady weight and frequency of activity from V1 to V3. When separating the lipid parameters on frequency of physical activity, there is a gradient showing that the patients who are the most active, have the best blood parameters. Although there are only a few participants in the low frequency training category, this is clear trend, and correspond to the inverse association stated by the WHO.

These improvements in lifestyle are probably the reason for the lack of weight gain in our selection. The treatment given at the Lipid clinic focuses greatly on lifestyle factors. The patients also reported at V3 that they were considering lifestyle to be equally as important as was their medication.

5.2.4 Comparison of CVD risk factors in CVD vs non-CVD individuals

Despite today's advancements, FH-patients are still affected by early CVD (125). Among our patients on V3, 31.3 % have experienced a CVD event. Other studies on FH patients have shown a prevalence of CVD in more than 37 % (118).

When comparing the CVD and no CVD patient groups, several of the differences seen in our variables were not found to be statistically significant. This is most likely due to the low number of participants in our sample, leading to a low statistical power. Even through, our findings are still clinically relevant.

Jansen et al found the classical risk factors age, male gender, smoking, hypertension, DM, HDL and Lp(a) to be of special importance to CVD risk in FH patients (46). All these except maybe HDL, was also confirmed in our sample of the TTTFH study as well.

There was a significant higher age among those who have developed CVD, and those who have not. Although there was a clear difference in the distribution of genders in the two

groups, this only borderline towards a trend ($p=0.100$) of a higher number of males with CVD, most likely due to the low participant number in this group.

There are slightly more CVD patients with side effects than in the non-CVD group. Not one patient in this group had treatment target reached as the reason for not increasing their medication dose. They had a slightly larger proportion of patients who did not wish to increase the dose, who had side effects and who already maximal medication than the non-CVD group.

Although, there was a higher percent of current smokers in the CVD group, there was not found significant difference compared to the non-CVD group. But, the number of years of smoking, combining both active smokers and former smokers, was significantly different, with a median of six years of smoking in the non-CVD group against 21 years in the CVD group.

The CVD group also had a significantly larger fraction of patients with hypertension and higher systolic blood pressure. The number of DM cases in the CVD group was that more than twice as big non-CVD group. Although not significant, this equals a higher percentage of DM among the CVD participants, and they showed also a significant higher on fasting glucose and HbA1c. The waist circumference was significantly larger among the CVD patients, and the median BMI was slightly higher than for the no CVD, although not reaching significance. A large waistline circumference, hypertension, and a fasting glucose above 6.5 mmol/l are associated with the metabolic syndrome. This indicates a possibility for a more frequent metabolic syndrome among the patients in the CVD group.

Patients were categorized based on whether they were using anti-diabetic and/or antihypertensive medication. Anti-diabetic drugs may reduce the progression of microvascular disease, but do not have any effect on macro vascular disease (126), hence the relationship between diabetes and risk of atherosclerosis should not be influenced.

Antihypertensive drugs on the other hand may decrease the CVD risk, and might weaken the hypertension-CVD difference between our two groups.

The CVD group had a more negative median profile on all blood parameters, although only a few medians were significantly different from the no CVD patients'. As there was found no significant difference in LDL, but a trend towards a difference in apo B, this might indicate a

larger proportion of small LDL particles in the CVD group. In previous studies on FH patients, LDL has not always emerged as a risk factor (127). Due to the comparison with others with similarly high LDL, one is not achieving enough power to observe an effect. Once comparing with non-FH controls, LDL emerges as a significant risk factor (127).

In addition to the possible smaller LDL particles, the CVD patients in our sample exhibit a non-significant, but lower HDL median and somewhat higher TG median that might indicate a slightly less favourable lipoprotein profile in the CVD group, although the medians are not outside of what is recommended. This indicates that in the CVD group there is a tendency to combined hyperlipidaemia. Since they also have larger waistline and higher BMI, the frequency of metabolic syndrome probably are increased among the CVD group.

The median Lp(a) score in the CVD group was more than twice the risk limit of 300 mg/L used in clinic. There was also a trend towards the CVD group having a higher median level of Lp(a) than the non-CVD group, where the median Lp(a) was beneath the risk limit. This will contribute in increasing the risk in the CVD group compared to the non-CVD group.

The CVD group had a higher untreated TC, but a lower untreated LDL. This is most likely due to a higher share of missing in these two variables, hence having different sets of individuals who made up each of the variables.

Entire 19 of the 20 CVD patients were on high intensity statin therapy, none on medium intensity statin therapy, and one person did not take any medication due to personal reasons. In the non-CVD group a lower fraction was on high intensity statin therapy, 8 (12.5) were on medium intensity statin therapy, and one person did not take any medication. This difference was not significant, again probably due to the low number of participants. The patients in this group of medium intensity statin therapy and non-CVD have a milder variant of FH.

When looking at cholesevelam, on the other hand, there was a trend towards a higher part of the CVD group receiving this drug. This is probably indicating a more serious FH with a more frequent use of triple medication to try to reach low LDL as possible. Comparing the Smart Diet scores, showed that the no- CVD group had slightly higher total score, and also more participants in the top category. A larger percentage had a higher fruit and vegetable intake, as well as doing more physical exercise and keeping a higher intensity of exercise. Those in the CVD group that were regularly working out were doing so in a quite frequent

manner. The CVD group scored slightly better on the choices of dairy products. None of these trends was found to be significant.

6 Conclusion

In the present study we found for the FH study population as a whole:

1. It is possible to reduce the median lipid values to the levels somewhat lower than in the ordinary Norwegian population through intensive medical combination therapy and a healthy lifestyle. Still there are only 15 (23.4 %) of the patients who reach their ESC/EAS guidelines treatment target at V3.
2. There were slightly fewer heavy smokers and smokers in general on V3 compared to V1, and there were slightly more participants who were physically active 3 times or more per week, and all participants were also only moderate alcohol consumers compared to V1. However, none of this was significant changes. Diet, on the other hand, was the only lifestyle variable that was significantly improved during these eight years of the TTFH-study. This was reflected in a higher total Smart Diet score, and an improvement in Smart Diet categories, i.e. in the intake frequency of vegetables and fish, and in the everyday choices made concerning dairy and meat products.
3. Concerning the medical treatment of our study population, 54 (84.4%) was on high intensity statin therapy with a considerable fraction also receiving dual or triple lipid medication (i.e. combination of statin, ezetimibe and coleselam). Rosuvastatin and atorvastatin as the main choices of statin. Side effects and intolerance of medication might be a problem for as many as 24 (37.5 %).
4. In our population of mean age of 52.1 years, 20 (31.3 %) had experienced a CVD event. This is premature CVD and an increased risk compared to the general Norwegian population. There might be a larger percentage of our patients that have DM, than in the general population, although this is hard to estimate due to lack of data for the latter. Hypertension was found to be as common as in one third of our study population.
5. Concerning the patients' treatment preferences there has been a slight shift, although not significant, towards the attitude that "lifestyle is considered to be equally important as the medication" by almost the entire study population on V3. There was further a high desire among the patients for "their cholesterol level to be as low as

possible”. This was weighted heavier than “to have no side effects” by 60 % of the participants at the start of the observation period at V1. Over the eight years this changed significantly, and on V3 less than 40 % agreed to that statement.

Further in the present study we found by comparing those who had experienced a CVD event against those who had not, that:

6. The CVD group had a more negative median profile on all blood parameters, although only a few medians were significantly different from the no CVD patients’, namely fasting glucose and HbA1c, and a trend towards a significant difference in Lp(a). There was found no significant difference in LDL, but a trend towards a difference in apo B. This could maybe indicate a larger proportion of small LDL particles in the CVD group.
7. The only lifestyle variable found to be significantly different between the two groups was the number of years smoking, which was more than three times longer for the CVD group. The non-CVD group had a slightly larger fraction scoring better on the Smart Diet. There was a slightly larger fraction of the CVD group who was physically active for three times or more per week compared to the non-CVD patients.
8. There are slightly more CVD patients with side effects than in the non-CVD group. No patients in this group reached the treatment targets. They had a slightly larger proportion of patients who did not wish to increase the treatment doses, or already used maximal medication.
9. In the group of CVD patients, there were significantly more individuals with hypertension than in the non-CVD group. There was also a larger percentage with DM, although not significant.

In conclusion, under favorable conditions adapted to each single patient through the specialized treatment at the Lipid clinic, the patients have improved or maintained nearly all of the measured variables, many of these standing in contrast to the general population. Still, as the larger part of the study group does not reach the treatment targets due to considerable side effects from the medication or they receive full doses which have insufficient power to reach the treatment targets, the search for other treatment alternatives is of essence. When looking into what characterizes the individuals that developed CVD in our study population,

we document the importance of the treatment obtained LDL-levels in combination with the number of classical risk factors among the patients. Those who lead a healthier lifestyle had less comorbidity, were fortunate to both have lower severity of side effects and to respond better to medication, and seemed, as a group to be less affected by CVD.

In this thesis we have observed indications that FH patients might be leading a healthier lifestyle on many points than the rest of the population. Future studies should be directed at identifying socioeconomic factors, known to be correlated with enhanced compliance, and whether the population of this study is different in any perspective from the FH patient group as a whole. This follow up has generated new descriptive knowledge on the effect of a maximally aggressive lipid lowering treatment and lifestyle intervention in a real life setting on FH patients in the Norwegian Lipid clinic. Hence it has generated a basis for further research.

Our future perspectives are first and foremost to complete V3 for the whole TTTFH study population, as well as proceeding with new follow up visits in the future. For this, there should be looked closer at the differences in how long the patients have been treated at the Lipid clinic, and how this affects their results. We also have to pay special attention to the drop out patients, and those who have left the study program, as this study has not taken this into consideration.

New highly potent lipid medication will soon be taken into use in the clinic (the PCSK9-inhibitors), and it will be of great interest to investigate the effect this will have on our patients' ability to reach their treatment target, hence lowering their CVD risk.

7 Conflict of interest

Sanofi Avensis has contributed financially to this project in order to free doctoral resources towards the targeted consultations conducted according to this study protocol. Sanofi Avensis has not had any impact on either the design of the protocol, planning of the study, implementation of the study or the compilation, interpretation and calculation of results, discussion or conclusion.

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Appendices

Appendix 1 Approval by the Regional Committee for Medical and Health Research Ethics

Appendix 2 The Doctor's Scheme

Appendix 3 The Smart Diet Questionnaire

Appendix 4 The Patients' Preferences Scheme

Appendix 5 Invitation with consent

Region: REK sør-øst	Saksbehandler: Anette Solli Karlsen	Telefon: 22845522	Vår dato: 20.05.2014	Vår referanse: 2014/753/REK sør-øst A
			Deres dato: 08.04.2014	Deres referanse:

Vår referanse må oppgis ved alle henvendelser

Kjell-Erik Arnesen
Oslo universitetssykehus HF

2014/753 Treat To Target Familiær Hyperkolsterolemi – Livsstil (TTT-FH - Livsstil)

Forskningsansvarlig: Oslo universitetssykehus HF

Prosjektleader: Kjell-Erik Arnesen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 08.05.2014. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektbeskrivelse

Hensikten med prosjektet er å undersøke prognosene til pasienter med familiær hyperkolesterolemi (FH) 8 år etter at de deltok i kvalitetssikringsprosjektet Treat to Target FH (TTT-FH).

FH er en arvelig sykdom som medfører redusert opptak av LDL-kolesterol fra blodet og nedsatt nedbrytning av kolesterol. Tilstanden medfører økt blodkolesterol og dermed økt risiko for koronar hjertesykdom. Treat To Target familiær hyperkolesterolemi (TTT-FH) er et prosjekt der data fra pasienter som går til oppfølging ved Lipidklinikken ved Rikshospitalet etter samtykke har inngått i et kvalitetsregister godkjent av Datatilsynet. Opplysninger som inngår i registeret er lipidverdier, behandlingsintensitet, bivirkninger av behandling og medisinering samt hjerte- og kar lidelser. Deltakerne ble inkludert i 2006 og 2007, og har siden vært til oppfølging en gang, i 2008. En ytterligere oppfølging er planlagt i 2014. Data fra oppfølgingsbesøkene skal inngå i kvalitetsregisteret.

I denne studien, som skal utgå fra kvalitetsregisteret, er det planlagt benyttet data fra et bekvemt utvalg på 50 til 100 personer som registreres ved standard oppfølging og klinisk undersøkelse. I tillegg skal det registreres opplysninger om kost og livsstilsfaktorer som er av betydning for FH ved intervju. Dersom deltakeren ønsker det, kan intervjuet skje per telefon. Deltakerne skal forespørres ved invitasjon per post, og det er planlagt å purre de som ikke svarer.

Primært endepunkt for denne delstudien er å kartlegge hvordan livsstilsfaktorer virker inn på lipidverdier og sykelighet over tid.

Dette skal undersøkes ved å beskrive hvorvidt livsstilsfaktorer (kost-, mosjons-, alkohol- og røykevaner) har endret seg i tiden fra 2006 til 2014, hvilke faktorer er viktige for de oppnådde lipidverdier (type statin, dose statin og livsstilsfaktorer), og hvorvidt det er sammenheng mellom typen behandling og forekomsten av nye hjerte- og karhendelser i oppfølgingsperioden.

Komiteens vurdering

Av søkeradsskjemaet og protokollen fremkommer det at det planlegges å benytte data fra alle deltakerne i kvalitetsregisteret i omsøkte delstudie, selv de som ikke responderer på utsending av invitasjon. Av det vedlagte informasjonsskrivet kan det videre forstås som at det i prosjektet er planlagt innhentet stedfortredende samtykke for bruk av opplysninger. Komiteen anser en slik tilnærming som problematisk, og kan ikke godkjenne at det anvendes data i prosjektet uten et det er innhentet spesifikt samtykke til dette. Det bes om at delen med stedfortredende samtykke strykes fra samtykkedelen av informasjonsskrivet.

Vedtak

Komiteen godkjenner prosjektet i henhold til helseforskningsloven § 9 og § 33 under forutsetning av at ovennevnte vilkår oppfylles. Godkjenning er gitt under forutsetning at det kun inkluderes opplysninger fra de som samtykker i denne delstudien.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søkerad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Det bes om at revidert informasjonsskriv innsendes til arkivet.

Godkjenningen gjelder til 31.01.2015.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal oppbevares av identifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektorats veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding på eget skjema, jf. helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søkeraden, må prosjektleder sende endringsmelding til REK, jf. helseforskningsloven § 11.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Anette Solli Karlsen
Komitesekretær

Kopi til: oushfdlgodkjenning@ous-hf.no

SCREENINGNR: _____

INITIALER: _____

DATO_____

TTTFH: Visitt 3

SIDE 1

MEDIKASJONHar det vært endringer i medikasjon siden forrige visitt: Ja Nei

Medikament/Helsekost etc (navn)	Grunn, indikasjon	Startet dato dag/mnd/år	Sluttet dato dag/mnd/år	Brukes fortsatt JA
				<input type="checkbox"/>

Bivirkninger av lipidmidler**Har pasienten bivirkninger:** 1. sikkert, 2. sannsynlig, 3. mulig, 4. nei

Hvis 1-3, fyll ut:

Medikament _____

Bivirkning 1-3 _____

Type, beskriv _____

Øker du lipidmedisineringen for å oppnå behandlingsmål: 1. Ja 2. Nei**Hvis nei - grunnene til ikke å øke medisineringen:**

- 1) Pasient vil ikke/ er skeptisk etc
- 2) Behandlingsmål nådd
- 3) Bivirkninger
- 4) Legen ser det an (kostsvikt, annen variasjon), nye prøver 6 uker
- 5) Legen vil ikke ut fra samlet vurdering (mulige bivirkn, interaksjonsfare, mange medisiner allerede, ikke alvorlig familierisiko, pasientens holdning etc)
- 6) Annet beskriv _____

Dato _____ Lege sign _____

TTTFH:

Visitt 3

SIDE 2

ADVERSE EVENTSIngen medisinske hendelser siden forrige visitt:

Bruk helst diagnoser, ikke individuelle symptomer, hvis mulig

Adverse event				
Startdato	(dd/mmm/åååå)	(dd/mmm/åååå)	(dd/mmm/åååå)	(dd/mmm/åååå)
Alvorlighet	<input type="checkbox"/> 1 Mild <input type="checkbox"/> 2 Moderat <input type="checkbox"/> 3 Alvorlig	<input type="checkbox"/> 1 Mild <input type="checkbox"/> 2 Moderat <input type="checkbox"/> 3 Alvorlig	<input type="checkbox"/> 1 Mild <input type="checkbox"/> 2 Moderat <input type="checkbox"/> 3 Alvorlig	<input type="checkbox"/> 1 Mild <input type="checkbox"/> 2 Moderat <input type="checkbox"/> 3 Alvorlig
Tiltak Lipidmedisiner ble	<input type="checkbox"/> 1 Øket <input type="checkbox"/> 2 Redusert <input type="checkbox"/> 3 Stoppet midlertidig <input type="checkbox"/> 4 Stoppet permanent	<input type="checkbox"/> 1 Øket <input type="checkbox"/> 2 Redusert <input type="checkbox"/> 3 Stoppet midlertidig <input type="checkbox"/> 4 Stoppet permanent	<input type="checkbox"/> 1 Øket <input type="checkbox"/> 2 Redusert <input type="checkbox"/> 3 Stoppet midlertidig <input type="checkbox"/> 4 Stoppet permanent	<input type="checkbox"/> 1 Øket <input type="checkbox"/> 2 Redusert <input type="checkbox"/> 3 Stoppet midlertidig <input type="checkbox"/> 4 Stoppet permanent
Hvilken lipidmedisin	_____	_____	_____	_____
Annen medik ble gitt	<input type="checkbox"/> Ja <input type="checkbox"/> Nei			
Annet/opr etc	_____	_____	_____	_____
Ingen tiltak	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do serious criteria apply?	<input type="checkbox"/> Ja <input type="checkbox"/> Nei			
Outcome, still present?	<input type="checkbox"/> Ja <input type="checkbox"/> Ukjent <input type="checkbox"/> Nei- løst	<input type="checkbox"/> Ja <input type="checkbox"/> Ukjent <input type="checkbox"/> Nei- løst	<input type="checkbox"/> Ja <input type="checkbox"/> Ukjent <input type="checkbox"/> Nei- løst	<input type="checkbox"/> Ja <input type="checkbox"/> Ukjent <input type="checkbox"/> Nei- løst
Dato løst	(dd/mmm/åååå)	(dd/mmm/åååå)	(dd/mmm/åååå)	(dd/mmm/åååå)
Årsak AE skyldes lipidmidler	<input type="checkbox"/> 1 Ja, sannsynlig <input type="checkbox"/> 2 Ja, mulig <input type="checkbox"/> 3 Nei, usannsynlig <input type="checkbox"/> 4 Nei, sikkert	<input type="checkbox"/> 1 Ja, sannsynlig <input type="checkbox"/> 2 Ja, mulig <input type="checkbox"/> 3 Nei, usannsynlig <input type="checkbox"/> 4 Nei, sikkert	<input type="checkbox"/> 1 Ja, sannsynlig <input type="checkbox"/> 2 Ja, mulig <input type="checkbox"/> 3 Nei, usannsynlig <input type="checkbox"/> 4 Nei, sikkert	<input type="checkbox"/> 1 Ja, sannsynlig <input type="checkbox"/> 2 Ja, mulig <input type="checkbox"/> 3 Nei, usannsynlig <input type="checkbox"/> 4 Nei, sikkert
Hvis nei, var årsaken Kardiovaskulær sykdom type:	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja
Annen sykdom type:	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja
Annen medikasjon (concomitant) type:	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja
Annet beskriv:	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja	<input type="checkbox"/> Ja

Har det vært potensielt endepunkt siden forrige visitt: Ja Nei (eget skjema)

SCREENINGNR: _____

INITIALER: _____

DATO_____

TTTFH:

Visitt 3

SIDE 3

SOSIALT

Endringer siden forrige visitt: † Ja † Nei

Skoleelev <input type="checkbox"/>	Student/lærling <input type="checkbox"/>	Fulltids jobb <input type="checkbox"/>	Deltidsjobb <input type="checkbox"/>
Hjemmeværende <input type="checkbox"/>	Sykemeldt <input type="checkbox"/>	Attføring/rehabilitering etc <input type="checkbox"/>	
Arbeidsledig <input type="checkbox"/>	Delvis uførepensjon <input type="checkbox"/>		
Bor alene <input type="checkbox"/>	Samboer/gift <input type="checkbox"/>	Bor med foreldre/søskjen/annen slekt <input type="checkbox"/>	

KOST

Endringer siden forrige visitt: † Ja † Nei

Poeng Smart diet _____ KEF i dag Fått skriftlig materiale i dag **RØYKING**

Endringer siden forrige visitt: † Ja † Nei

Aldri røykt <input type="checkbox"/>	Tidligere røykt <input type="checkbox"/>	Startet første gang _____	Sluttet siste gang _____
Sigaretter røyker <input type="checkbox"/>		Antall per dag _____	
Pipe/cigarillos røyker <input type="checkbox"/>		Antall per dag _____	

ALKOHOL

Endringer siden forrige visitt: † Ja † Nei

Enheter per uke _____

TRENING

Endringer siden forrige visitt: † Ja † Nei

Type _____	Tid per uke _____
Type _____	Tid per uke _____
Type _____	Tid per uke _____

FEMALE OF CHILDBEARING POTENTIAL Ja NeiHvis JA, prevensjon: P piller Annet _____ IntetHvis NEI, hvorfor: ≥ 2 år siden menopause Annet _____ Sterilisert**MEDIKAMENT ALLERGI** Ja Nei

Hvis JA, hvilken prevensjon: Medikamentnavn/klasse

Type reaksjon

Hvis det er potensielt endpunkt, fyll ut:

Page _____

	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	F M L	<input type="text"/> <input type="text"/> <input type="text"/>	dd MMM yyyy
SUBJECT	NO.	INITIALS			DATE OF VISIT

POTENTIAL ENDPOINTS

Please fill out one form per endpoint (check only one box)

- | | |
|---|---|
| <input type="checkbox"/> Suspected or Confirmed Non Fatal Acute MI | <input type="checkbox"/> Hospitalization with Primary Diagnosis of CHF |
| <input type="checkbox"/> Death - Coronary | <input type="checkbox"/> Cerebrovascular Event |
| <input type="checkbox"/> Death - Other | <ul style="list-style-type: none"> • Fatal stroke • Non-fatal stroke • TIA |
| <input type="checkbox"/> Coronary Revascularization Procedure <ul style="list-style-type: none"> • Coronary artery bypass graft (CABG) • PTCA (includes atherectomy and stent implantation) • Other coronary revascularization procedure | <input type="checkbox"/> First Diagnosis of PVD |
| <input type="checkbox"/> Documented Angina | <input type="checkbox"/> Hospitalized PVD Event |
| | <input type="checkbox"/> Other Non-CHD Vascular Events |

Date of Event:

<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>
dd	MMM	yyyy

If hospitalized, check one:

Only seen at Emergency Room/
Causality Dept/Outpatient Clinic:

Admitted to:*

Specify site:*

* Include facility name, street address, city and country.

Admission Date:

<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>
dd	MMM	yyyy

Discharge Date:

<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>
dd	MMM	yyyy

Date:
dd MMM yyyy

Investigator's Signature: _____ Monitor: _____

SmartDiet

20 spørsmål om ditt kosthold og din livsstil

Copyright: Lipidklinikken®, Rikshospitalet

Du får først 15 spørsmål om ditt kosthold og deretter 5 spørsmål om din livsstil.

Les spørsmålene og de angitte svarmulighetene nøy!

Angi gjerne hva du spiser med en strek under matvaren(e).

Sett kryss ved det svarer som passer best med gjennomsnittet av dine spisevaner.
Gi kun ett svar til hvert spørsmål.

1. Melk (surtsøt)

Hvor mange glass melk drikker / bruker du daglig? Antall: _____

- Hvilken type bruker du oftest? Som drikk, på gryn, grøt, dessert, i kaffe/te.
Hjemmelk • Kulturmelk • Kefir • Kaffemelk 5% fett
Lettmelk • Cultura • Biola (syret lettmelk) • Ekstra Lett melk
Skummet melk • Skummet kultur melk • Biola bærdrikk (0,1% fett)
Drikker / bruker melk sjeldent eller aldri

2. Fløte, rømme og lignende

Hvilken type bruker du oftest? I matflaging, i kaker, i kaffe, i te, som dressing o.l.

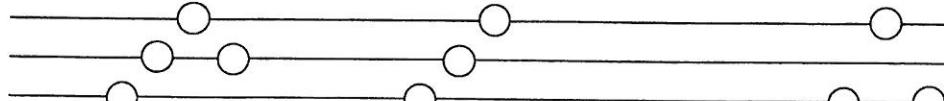
- Kremfløte • Pisket krem • Crème Fraîche • Seterømme
Kaffefløte • Matfløte • Vikingmelk • Kream (8% fett) • Rømmekolle • Lettrømme
Bruker fløte eller rømme én gang eller sjeldnere i uken

3. Brød, knekkebrød og andre kornprodukter

Hvor mange skiver brød/ knekkebrød eller porsjoner kornblanding spiser du daglig?
Antall: _____

Hvor mange måltider med fine kornprodukter spiser du?

- "Vanlig" kneipp • finbrød • fint hjemmebakt og kjøpe brød • løff • fine rundstykker • lyst knekkebrød • baguetter • riskaker • puffert ris • cornflakes • havrefløter • frokostkorn (med sjokolade, honning, sukker o.l.)
Mer enn 4 måltider i uken
- Mindre enn 4 måltider i uken
- Spiser ikke brød / knekkebrød eller andre kornprodukter.....



Navn:
Fødselsdato:
Dato for besvarelsen:

4. Smør, margarin på brødmaten

Hvilken type bruker du oftest?

Meierismør • Tine smør (mykere) • Tine setersmør • Smøregod • Bremyk • Brelett •

Melangemargarin • Per margarin • Soft flora stekemargarin (kübe) • Soya stekemargarin (kübe) •

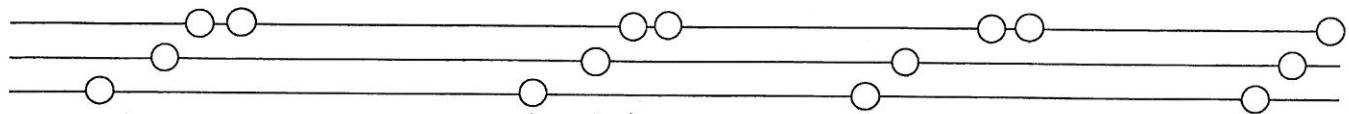
Soft margarin uten salt og melk • Letta

Soft Flora (beger) • Soft Light • Soya margarin (beger) • Soya lett margarin • Olivens margarin •

Olivero • Solsikke margarin

Vita • Vita lett • Omega

Bruk vanligvis ikke smør eller margarin på brødmaten



5. Ost på brødmaten, i matlagning og på pizza o.l.

Hvor mange skiver brød / knækkebrød med ost spiser du daglig? Antall: _____

Hvilken type bruker du oftest?

Hvitost (F45) • Nøkkkelost (F45) • Gudbrandsdalsost (G35) • Ekte geitost • Fløtemysost • Edamer • Gräddost • "Dessert ostet" • Smørbar fete ost (H50 og fetere) • Mozzarella (mer enn 20% fett) • Feta ost (mer enn 20% fett) • Revert pizza-/pastaost • Taffelost •

Burgerost • Snøfrisk, smørbar geitost • Parmesan

Leitere hytost • Leitene nøkkelost • Lettere fløtemysost • Lettere Gudbrandsdalsost • Smørbar ost (16% fett) • Mozzarella (16% fett) • Fetaost (20% fett) • Prim med vaniljesmak

Cottage cheese • Gamlastost • Pultost • Mager mysost • Prim • Mager prim • Smørbar magerost

Bruk ost to ganger eller sjeldnere i uken, eller bruker aldri ost

6. Kjøtt pålegg

Hvilken type bruker du oftest?

Leverpostei • Salami • Lett salami/spesialsalami • Servelat • Fårepølse • Fåtulkorv • Flestepølse • Morrpølse • Reinsdyrpølse • Stabbumpølse • Syte • Lammerull

Leit/mager leverpostei • Leitt servelat • Delikat ovnsbakt postei

Bankekjøtt • Kalkunkpålegg • Kyllingpålegg • 3% servelat (Det Sunne Kjøkken) • 3% leverpostei (Det Sunne Kjøkken) • Kalverull • Okserull • Skinkekoktrotkt

Hamburgerrygg • Annet kjøtt uten synlig fett

Bruk ikke kjøtt pålegg ukentlig eller bruker aldri kjøtt pålegg

7. Fiskepålegg

Hvor ofte har du fiskepålegg på brødmaten?

Laks • makrell • sild • sardiner • brisling • tunfisk • reker • krabbe • crab-sticks • fisrepudding • fiskeraker • Havbris etc.

På inntil 1 brødkive i uken, eller aldri

På 2 til 4 brødkiver i uken

På 5 eller flere brødkiver i uken

8. Majones, majonespålegg

Hvor ofte har du majonespålegg på brødmaten?

Majones • Rekesalat • krabbesalat • frokostsalat • italiensk salat o.l.

På inntil 1 brødkrive i uken, eller aldri

På 2 til 7 brødkiver i uken

På 8 eller flere brødkiver i uken

9. Kjøtt til middag

Hvilken type bruker du oftest?

Også medregnet kjøtt i sammensettete retter som pizza, lasagne, pastareitter, gryteretter, lakskaus, taco og lignende og bacon til frokost

- Grillpølse • Wienerpølse • Kjøttbølse • Knakkpølse • Nakkekoteletter med fettrand • Lammekoteletter • Medisterfarse • Medisterpølse • Medisterdeig • Medisterkake • Wienerschritzel • Fenalar • Bacon med fettrand • Flesk • Grillben • Færkjøtt • Pinnekjøtt • Ribbe • And • Gås

- Kjøttdig • Kjøttkaker • Kjøttpudding • Kjøpte karbonader • Hamburger • Kebabkjøtt • Lettpølse • Kyllingpølse • Kamkoteletter med fettrand • Nakkekoteletter uten fettrand • Kylling med skinn • Høne med skinn • Kalkun med skinn • Blodpudding • Bayonneskinke med fettrand • Hamburgerrygg med fettrand

- Kjøtt uten synlig fett • Karbonadedeig • Biff • Stek uten fettrand • Bogskinke • Kamkoteletter uten fettrand • Pølser, Falukorv, Kjøtpudding og Karbonader med 3% fett ("Det Sunne Kjøkken") • Grill- og kjøttbølser med 9% fett ("Go' og Mager" fra Gilde) • Viltkjøtt • Kalv • Lam indreflet • Høne uten skinn • Kylling uten skinn • Kalkun uten skinn

Spiser ikke kjøtt ukentlig, eller aldri

10. Fisk til middag

Hvor mange ganger i uken spiser du fersk fisk, fiskemat og/eller fiskeretter?

Inntil en gang i uken eller aldri

2 ganger i uken

3 eller flere ganger i uken

11. Fett i matlagingen

Hvilken type fett bruker du oftest? I matlaging; steking, baking, i saus.

- Meierismør • Tine smør (mykere) • Tine setersmør • Bremyk • Smøregod • Melange margarin (kub) • Per margarin (kub) • Soft Flora stekemargarin (kub) • Soya stekemargarin (kub)
- Soft Flora (beger) • Soya margarin, (beger) • Solsikke margarin • Oliven margarin • Olivero Olie • Flytende margarin • Vita • Omega
- Bruker vanligvis ikke fett i matlagingen

12. Grønnsaker

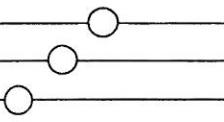
Hvor mange portioner grønnsaker, kokte og/eller rå, inkludert poteter, spiser du daglig?

1 portion = 150 g: 2 dl grønnsakblanding, 3 dl blandet salat, 2 gulrøter, 2 poteter o.l.

0 til 1 daglig

2 daglig

3 eller flere



13. Frukt, bær, juice

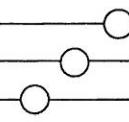
Hvor mange portioner spiser/drikker du daglig?

1 portion = 150 g: 1 appelsin, 1 eple, 20 druer, 2 dl bær, 1,5 dl juice o.l.

0 til 1 daglig

2 daglig

3 eller flere daglig



14. Sukker, søtt pålegg og sot drikk

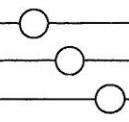
Hvor ofte spiser/drikker du dette?

1 brødskive med honning, syltetøy, prim, brunost, sjokoladepålegg eller annet sot pålegg; 1 glass sukkret saft, brus, juice eller nektar, 5 sukkerbiter, 1 skje sukker

0 til 2 ganger daglig

3 til 4 ganger daglig

5 eller flere ganger daglig



15. Godteri, sjokolade, snacks, kaker, fet kjeks, iskrem

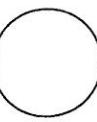
Hvor ofte spiser du dette?

Bortsett fra: Nøtter • mandler • marsipan • hjemmepoppet popcorn • sukkerfrie godterier • vingummi • drops • pastiller • magjer bakst (som gjærbakst) • safis, yoghurtis, sorbet

1 gang i uken eller sjeldnere

2 til 3 ganger i uken

4 eller flere ganger i uken



Antall poeng:

5 spørsmål om din livsstil

Kjønn Mann Kvinne
Alder _____ år
Høyde _____ cm
Vekt _____ kg

1. Vekt

Jeg ønsker å gå ned i vekt Nei Ja

2. Røyker du?

Nei Ja Ja, selskapsrøyker

Hvis ja, hvor mange sigareetter/piper røyker du per dag?

- Mindre enn 1
 1 til 5
 6 til 10
 11 til 20
 Mer enn 20

3. Drikker du alkohol?

Nei Ja

Hvis ja, hvor mange enheter alkohol drikker du til sammen per uke?

1 enhet =

- 1 glass vin (125 ml)
1 glass øl (0,33 l)
4 cl brennevín (drink, konjak, likør)

- Mindre enn 1
 1 til 7
 8 til 14
 Mer enn 15

4. Hvor ofte mosjonerer du i minst 30 minutter?

Rask gange, løping, skigåing, svømming, sykling etc.

- Aldri Sjeldnere enn 1 gang per uke
 1 til 2 ganger per uke 3 eller flere ganger per uke

5. Bruker du kosttilskudd?

- Nei Tran
 Fiskeoljekapsler/omega3-kapsler Multivitamin
 Annet: _____

Kostholdsvurdering

- 29 poeng eller mindre: Du bør forbedre kostholdet ditt på mange punkter for å gjøre det mer helse- og hjertevennlig
- 30 til 37 poeng: Du kan forbedre kostholdet ditt på en del punkter slik at det blir mer helse- og hjertevennlig
- 38 poeng eller mer: Du har sunne kostholdsvaner

Kommentarer:

Sporreskjemaet vil ikke nødvendigvis gi et komplett bilde av ditt kosthold. Du kan få mer kostholdsinformasjon i heftet "Kostbehandling ved høye blodlipider hos voksne" (*Lipidkliniken 2000*).

Skjemaet er vitenskapelig bedømt i forhold til veid kostholdsregistrering, med unntak av spørsmål 14 om sukker. Evalueringen ble publisert i tidsskriftet "Nutrition, Metabolism and Cardiovascular Diseases" i 2002.

Case id:

Intensiv pasientoppfølging – hvor fornøyd er du med det?

Kjære pasient!

I prosjektet forsøker vi med en svært tett oppfølging å senke kolesterolen til verdier som er lavere enn i normalbefolkningen.

Hensikten er her å få vite hva du mener om så intensiv oppfølging, om hvor fornøyd du er med det og hvilke ulemper det medfører.

Dato.....

1. Hvor får du hovedoppfølgingen av din FH?

- Fastlegen
- Sykehus
- Lipidklinikken
- Ingen

2. Hvor ofte er du hos fastlegen?

Antall ganger per år: _____

3. Hva synes du følgende utsagn: ***Jeg er fornøyd med oppfølgingen!***

- Helt enig
- Delvis enig
- Verken enig eller uenig
- Delvis uenig
- Helt uenig

4. Hvor ofte ønsker du å bli kontrollert for FH?

- 4 ganger årlig
- 2 ganger årlig
- 1 ganger årlig
- Sjeldnere
- Hyppigere enn 4 ganger årlig

5. Hva synes du om så tett oppfølging som det er nå i prosjektet?
(Kryss av på skalaen fra 1 til 10, hvor 1 er svært misfornøyd og 10 er svært fornøyd)



Økende fornøydhetsgrad →

Hva synes du følgende utsagn:

6. **Jeg stoler på at medikamentene i seg selv forhindrer at jeg får hjerteinfarkt**

Helt enig Delvis enig Verken enig eller uenig Delvis uenig Helt uenig

7. **Jeg synes ikke helsevesenet skal være så pågående når det gjelder FH**

Helt enig Delvis enig Verken enig eller uenig Delvis uenig Helt uenig

8. **Jeg tror sunn kost og livsstil er minst like viktig som riktig medisin**

Helt enig Delvis enig Verken enig eller uenig Delvis uenig Helt uenig

9. **Jeg ønsker at kolesterolverdien blir så lav som mulig**

Helt enig Delvis enig Verken enig eller uenig Delvis uenig Helt uenig

10. **Det er viktigere å ha lite eller ingen bivirkninger enn lav kolesterol**

Helt enig Delvis enig Verken enig eller uenig Delvis uenig Helt uenig

Hjertelig takk for innsatsen!

Forespørsel om deltakelse i forskningsprosjektet

"Treat To Target Familiær Hyperkolsterolemi - Livsstil"

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i oppfølgingen av den forsknings- og kvalitetssikringsstudien som du deltok i årene 2006-07, Treat To Target – FH studien. Man vil nå foreta en 8 års oppfølging, for å se hvordan det har gått disse årene både vedrørende intensivert behandling, lipidverdier, bivirkninger, risiko og hjertekarhendelser. Man vil fokusere på effekten av livsstilsendringene.

Hva innebærer studien?

Studien innebærer at du møter opp ved Lipidklinikken personlig, eller at du deltar ved et telefonintervju. Deltakere som ønsker en utvidet vurdering, vil få satt opp en poliklinisk time ved Lipidklinikken. Vi vil finne et tidspunkt som passer ved å sette deg opp til konsultasjon, og så å ringe deg. Konsultasjonen vil fungere som en vanlig lege- og klinisk ernæringsfysiolog kontroll.

Hvis du ønsker telefonintervju, vil bli spurtt om "de vanlige journalopplysningene" som blant annet vekt, høyde, blodtrykk, lipidverdier, allergier, kosthold, sykdommer i denne perioden, medikamentbruken og eventuelle bivirkninger av dem. Du vil også bli spurtt om å fylle ut SmartDiet, som du kjenner til, og vil få tilbud om en egen samtale med en trenet student i klinisk ernæringsvitenskap.

Dersom det er mer enn 6 måneder siden du sist målte lipidverdiene, eller dersom du har endret behandlingsopplegget siden forrige blodprøve, eller dersom tidligere prøver ikke inneholder alle blodprøvesvarene vi ser etter, vil du bli spurtt om å avgrense en ny blodprøve.

Fordeler og ulemper

Ulempen ved deltagelsen vil være forbruket av tid. Fordelen vil være at du får en ny gjennomgang av sykehistorien og behandlingsopplegget. Mange av vår pasienter har uforholdsmessig langt ventetid mellom kontrollene ved Lipidklinikken, ofte opptil 2-3 år. En ny gjennomgang med oppdatering om de siste nyhetene vedrørende medisiner, hjertesykdom, livsstil og om hva som rører seg i feltet, vil ofte være nyttig. Du vil få tatt opp dine dagsaktuelle problemer.

Hva skjer med prøvene og informasjonen om deg?

Informasjonen som registreres om deg, vil bli sammenfattet i vanlig klinisk journalnotat, og sendt til deg og dine leger, slik som tidligere. Data vil også bli registrert i en database, og bruk til forskning og forbedring av våre tiltak og rutiner. Forskningsopplysningene og prøvesvarene vil bli behandlet uten

navn og fødselsnummer, eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver ved en navneliste. Det er kun autorisert personell ved prosjektet som har adgang til navnelisten, og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien, når disse publiseres.

Frivillig deltagelse

Det er frivillig å delta i studien. Du kan når som helst, og uten å oppgi noen grunn, trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling ved Lipidklinikken. Ved fremtidige oppfølginger ved nye visitter i TTT-FH prosjektene, vil du bli forespurt. Det vil da bli innhentet nytt samtykke.

Dersom du ønsker å delta, må du undertegne samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg, eller har spørsmål til studien, så kontakt overlege Kjell-Erik Arnesen på telefon 23075613 eller mobil 92485970.

Ytterligere informasjon om studien finnes i kapittel A – utdypende forklaring av hva studien innebærer.

Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B – Personvern, biobank, økonomi og forsikring.

Samtykkeerklæring følger etter kapittel B.

Kapittel A- utdypende forklaring av hva studien innebærer

Kriterier for deltagelse

Voksne pasienter som tidligere har deltatt i TTT-FH prosjektets to konsultasjoner i 2006 og 2007, vil få forespørsel om deltagelse per brev og/eller per telefon.

Bakgrunnsinformasjon om studien

Familiær hyperkolesterolem (FH) er en arvelig tilstand hvor en genendring fører til redusert antall LDL-reseptorer. Det fører til et høyt kolesterol i hele livet. Tidlig og livslang kolesterolenkende behandling sammen med optimal og risikolav livsstil, forhindrer i betydelig grad åreforkalkninger. Man oppnår nærmest like god livsprognose som normalbefolkningen. Vi ønsker nå å etterundersøke deltakerne, for å bedømme effektene over en 8 års periode.

Undersøkelser, blodprøver og annet den inkluderte må gjennom

Se beskrivelse på side 1 under avsnittet: *Hva innebærer studien.*

Tidsskjema – hva skjer og når skjer det?

Konsultasjonen og intervjuene vil bli gjennomført i løpet av høsten 2014.

Kapittel B - Personvern, økonomi og forsikring

Personvern

Opplysninger som registreres om deg er ”vanlige journalopplysninger” som blant annet alder, kjønn, vekt, høyde, blodtrykk, lipidverdier, allergier, kosthold, sykdommer i perioden, medikamentbruk og eventuelle bivirkninger. Oslo Universitetssykehus Rikshospitalet ved administrerende direktør er databehandlingsansvarlig.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser, eller brukt i vitenskapelige publikasjoner.

Økonomi

Prosjektet gjennomføres av Lipidklinikken, og det er ingen økonomiske interesser i prosjektet. Man får dekket reiseutgifter slik som ved vanlig konsultasjon. Man betaler ikke egenandel, slik som ved deltagelse i forskningsprosjekter.

Forsikring

Da dette er en klinisk undersøkelse med intervjuer, er det ikke forsikring av studiedeltakere. Blodprøvetaking vil være ledd i vanlig poliklinisk oppfølging. Blodprøvetakingen er forbundet med svært liten risiko, men eventuelle skader vil måtte meldes til Norsk Pasientskadeerstatning og dekkes på vanlig måte for poliklinisk virksomhet.

Informasjon om utfallet av studien

Resultatene fra studien vil bli sammenskrevet og forsøkt publisert i et vitenskaplig tidsskrift. Et populærvitenskaplig sammendrag vil bli tilsendt deltakere etter publisering.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

(Navn med blokkbokstaver)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

(Navn med blokkbokstaver)