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Treat-To-Target Familial Hypercholesterolemia

Completion of a 10-12-years follow-up study on long-term effects of intensive lipid lowering treatment in FH patients at a specialized Lipid Clinic

Master's thesis by Ann Vinh Phung

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Master's thesis in Clinical Nutrition

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Summary

Background and aim: Familial hypercholesterolemia (FH) is a relatively common hereditary disease characterized by severely elevated cholesterol levels since birth, resulting in a seriously increased risk of premature cardiovascular disease (CVD) compared to the normal population. The aim of this thesis is to assess the long-term effects of intensive lipid lowering treatment in an outpatient lipid clinic (LC) over a period of 10-12 years. We want to describe the improvements in lipid values, diet and lifestyle, as well as the development of metabolic syndrome and cardiovascular disease during the project period. It is also of interest to compare different subgroups in the population.

Subjects and methods: The Treat-to-Target Familial Hypercholesterolemia (TTT-FH) study was initiated in 2006 with 357 adult FH-patients attending visit 1 (V1). Visit 2 was conducted one year later with 332 patients. During 2015-2019, four master's students conducted visit 3 (V3) part I-IV with a total of 279 patients. Data on medications, side effects, diet and lifestyle were collected through the SmartDiet form, blood samples and two specially developed forms for the project. The majority of the population were screened through routine consultations at the LC, while patients living outside of Oslo conducted telephone interviews with the student. Missing data were retrieved from the patients' medical records upon permission.

Results: Mean age at V3 was 55.2 years, and half of the population was male. Genetically verified FH was documented in 86.4%. The mean (95%CI) first known elevated total cholesterol (TC) level was 9.8 mmol/L(9.5, 10.1), and was measured at a mean age of 27.9 years. At V3, 28% were treated for hypertension, and 10% for diabetes. Weight, BMI, and waist circumference increased with 3 kg, 1.1 kg/m^2, and 4 cm, respectively. At V1, the mean TC on treatment was 5.7 mmol/L (5.5, 5.8), and LDL-C was 4.1 mmol/L (3.7, 4.6). After median (min,max) 10 (8.1, 12,8) years of further follow-up at the LC, the achieved mean TC and LDL-C was 4.9 (4.7, 5.1) and 3 mmol/L (2.9, 3.2), respectively. Altogether, 30.8% had cardiovascular disease (CVD), with a debut at mean age 47.6 (45.2, 50.1) years. At V3 metabolic syndrome (MetS) was diagnosed among 20.8% of the population. Of those with CVD, 39.8% had MetS, versus 13.3% among the patients with no CVD. High first measured cholesterol level, high age of first measured cholesterol level, high lipoprotein (a) levels, diabetes and hypertension are important risk factors of CVD in this study population.

Conclusion: Intensive traditional lipid lowering treatment resulted in modest favorable changes in lipid profiles from V1 to V3. The patients had a heart-friendly diet that was consistent through the whole study period. Still, the majority of the population did not reach their treatment targets with traditional maximal lipid lowering treatment. The prevalence of MetS was increasing in the population, with significant increases in weight, BMI and waist circumference. Those with CVD had a higher prevalence of MetS and hypertension, and were familiar with their hypercholesterolemia at a much older age compared to the healthy subjects. These results indicate a need of added novel therapies, e.g. PCSK9-inhibitors, in the treatment regimens to better reach the treatment targets. This study also highlights the importance of early detection and treatment initiation to prevent early development of CVD.

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Ann Phung

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95%CI	95% confidence interval
ACC/AHA	American College of Cardiology/American Heart Association
AMI	acute myocardial infarction
Apo B	apolipoprotein B
CAD	coronary artery disease
CHD	coronary heart disease
CRP	C-reactive protein
CTT	The Cholesterol Treatment Trialists' Collaboration
CVD	cardio vascular disease
CVD	cardiovascular
DLCN	Dutch Lipid Clinic Network
EAS	European Atherosclerosis Sociaety
ESC	The European Society of Cardiology
FH	familial hypercholesterolemia
GI	gastrointestinal
HDL	high-density Lipoprotein
HDL-C	HDL-cholesterol
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
hsCRP	high-sensitivity C-reactive protein
IDL	Intermediate-density lipoproteins
LC	Lipid clinic
LDL	low-density-lipoprotein
LDL-C	LDL-cholesterol
LDL-R	LDL-receptor
LDLRAP	low-density lipoprotein receptor adaptor protein
LIPA	lysosomal acid lipase

LLT	Lipid lowering treatment
MetS	Metabolic Syndrome
NIPH	Norwegian Institute of Public Health
NKT for FH	National advisory unit on familiar hypercholesterolemia
NO	nitrogen oxide
NSFA	Nouvelle Société Francophone d'Athéroslérose
OUS	Oslo university hospital
PCSK9	proprotein convertase subtilin/kexin 9
PNPLA5	patatin-like phospholipase-domain-containing family
PRIMO	Prediction of Muscular Risk in Observational conditions study
PROVE IT - TIMI 22	The Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22
SAMS	Statin associated muscle symptoms
SSB	Statistics Norway
STAP1	signal transducing adaptor protein family 1
T2D	Type 2 diabetes
TC	Total cholesterol
TG	Triglyserides
HUNT	The Nord-Trøndelag Health Study
Tromsø	The Tromsø Study
TTT-FH	Treat-to-target familial hypercholesterolemia
USAGE	Understanding Statin Use in America and Gaps in Patient Education survey
V1	visit 1
V2	visit 2
V3	visit 3
VLDL	very-low-density-lipoproteins
WHO	World health organization

1 Introduction

1.1 Atherosclerosis and cardiovascular disease

Atherosclerosis is the name of the complex process where arteries in the body are narrowed by built up plaques inside the artery walls (Figure 1), and the result is cardiovascular disease (CVD). The term "atherosclerosis" is made up from "athero" (gruel) and "sclerosis" (hardening) (1). It describes how plaque formation can block the blood flow to vital organs, such as the heart and the brain. CVD, a term for diseases affecting the heart and the circulatory system, is the number one cause of death worldwide (2). Together with cancer, CVD is the most important cause of death in Norway, and about 70 000 people are treated for CVD each year (3).

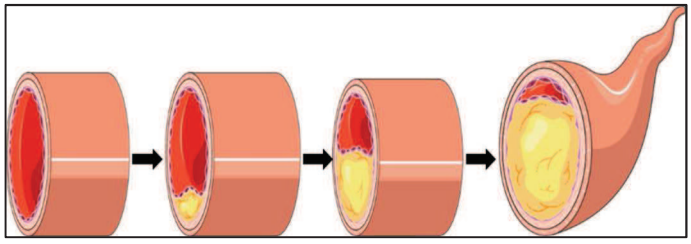

Figure 1: The atherosclerotic process.
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In 1950, Gofman et. al. demonstrated that the cholesterol containing lipoproteins could be separated into several groups based on their density. These groups are known as chylomicrons, very-low-density-lipoproteins(VLDL)/ Intermediate-density lipoproteins (IDL), low-density-lipoprotein (LDL) and high-density Lipoprotein (HDL) (4). Gofman et. al. further showed that the serum levels of LDL particles in the blood were higher in patients who have suffered from myocardial infarction compared to normal individuals. In 1957, The Framingham Heart Study in Massachusetts stated that hypertension and hypercholesterolemia were strongly associated with the development of arteriosclerotic heart disease (5). In a cohort study in Norway where 45 000 participants were followed over 25 years, the researchers showed that the age-adjusted relative risk of coronary heart disease (CHD)-related mortality increased with 30% and 40% per 1 mmol/L increase in total cholesterol for men and women, respectively (6). The Seven Countries study further confirmed that increasing levels of serum cholesterol is strongly associated with CHD, even across different cultures (7).

Cholesterol and the atherosclerotic process

Atherosclerosis is a multifaceted disease which involves both genetic and environmental factors, and is mainly found in the large and intermediate-sized arteries (8). The process may start early in life, and Palinski et. al. have shown that already during pregnancy, maternal

hypercholesterolemia increases fatty streaks, a precursor of atherosclerosis, in the arteries of the human fetus (9). High levels of LDL-cholesterol (LDL-C) in the bloodstream may lead to retention of LDL particles in the artery walls, with a following oxidation of the cholesterol. How the LDL particle enters the intima is an important question and a topic of intense research (10).

The oxidized cholesterol of LDL particles promotes infiltration of macrophages and increased production of different growth factors and cytokines inside the artery walls. In the subendothelial space, the monocytes will eventually form macrophages and subsequently foam cells upon consuming the oxidized LDL-C. The atherosclerotic plaque will further grow and narrow the blood passage, and potentially tear and give rise to a thrombus that may block the artery (11). Apart from the quantity of circulating LDL-C, the quality and composition of the LDL-C particle also contributes to the atherosclerosis process. Ruuth et. al. emphasizes that some LDL-C compositions are more prone to aggregate in the artery walls where several modifications, including oxidization, takes place (12). This in turn promotes foam cell formation and atherogenesis.

1.2 Familial hypercholesterolemia

1.2.1 Genetics, pathophysiology and diagnosis

Familial hypercholesterolemia (FH) is a relatively common hereditary disease characterized by severely elevated cholesterol levels since birth, with a much higher risk of premature CVD compared to the normal population (13, 14). The disease is autosomal dominant in a heterozygous (HeFH) or homozygous (HoFH) form, the former variant is the most common. FH is a disorder of the LDL-C metabolism, and defects in this metabolism determine the phenotype of FH. So far, researchers have found pathogenic mutations on four genes; the LDL-receptor (LDL-R), apolipoprotein B (Apo B), proprotein convertase subtilin/kexin 9 (PCSK9), and low-density lipoprotein receptor adaptor protein (LDLRAP), however, the latter is rare (15, 16). The field of FH and lipid diseases is constantly advancing, and new genes have been identified as possible FH-causing genes, like signal transducing adaptor protein family 1 (STAP1) , lysosomal acid lipase (LIPA) and patatin-like phospholipase-domain-containing family (PNPLA5) (16-19). These genes have yet to be confirmed as pathogenic.

Mutations in LDL-R

A single gene mutation in the LDL-R is the most common cause of FH. The heterozygous variant is less severe than the homozygous form, where the genes on both alleles coding for the LDL-R are defected in HoFH (20). The LDL-Rs are located on the surface of the cell membranes of hepatocytes, as well as on other cells throughout the body (8). The receptors have affinity to the LDL-C particles through apolipoprotein B-100, and initiates the uptake of the cholesterol particles in the cells (21, 22). The mutations in LDL-Rs are "loss of function mutations", where the receptors' ability to clear LDL-C from the blood is reduced, and the LDL-C level in the blood is elevated. The severity and clinical expression of FH varies according to the specific type of mutation.

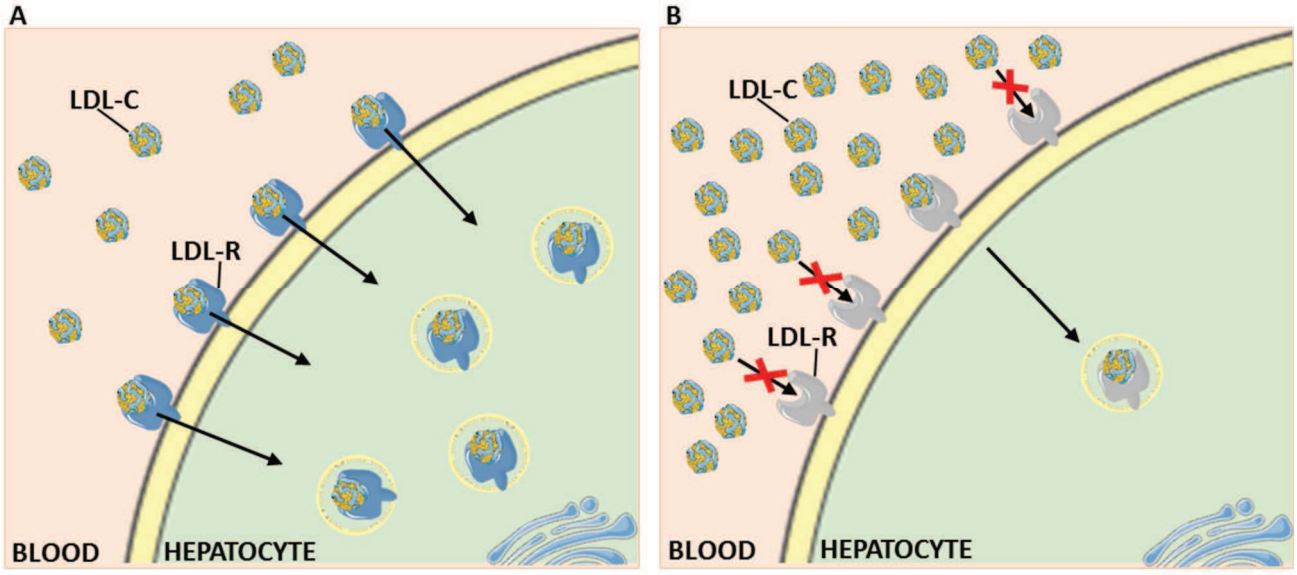

Figure 2a-b: The LDL-C uptake through LDL-R in hepatocytes.
A) Normal uptake of LDL-C in hepatocytes through binding to LDL-Rs on the cell surface. B) Loss of function mutation on LDL-R. The LDL-Rs have reduced affinity to LDL-C and have reduced uptake of LDL-C in the cell. This leads to accumulation of LDL-C in the circulation.
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Mutations in the Apolipoprotein B

Mutations in the ApoB-genes are also "loss of function mutations". The apoB-gene encodes for apolipoprotein B-48 and apolipoprotein B-100, in which both are important components in the lipoproteins (23). The ApoB-48 is synthesized in the intestine after food consumption, while the ApoB-100 is produced in the liver. A defect in the apolipoprotein B-100 causes the

LDL-C particle to no longer have affinity to the LDL-R, and the LDL-C remains in the bloodstream (24, 25) .

Mutations in the proprotein convertase subtilin/kexin 9 enzyme

The PCSK9 enzyme is synthesized and secreted by the liver. Its functions are involved in the degradation of the LDL-R, wherein PCSK9 targets the receptors that are to be degraded (26, 27). LDL-Rs that are not targeted by PCSK9 will be re-used on the cell surface for uptake of LDL-C particles. A "gain of function mutation" of PCSK9 will lead to increased degradation of the LDL-R, and therefore increased levels of LDL-C in the blood (28, 29). "Loss of function mutations" will lead to lower LDL-C levels and act protective against CHD (30).

Diagnosis and tools

Because of the dominant hereditary properties of the disease, the doctors often draw a family pedigree during the consultation. Markedly elevated cholesterol levels, physical findings like tendon xanthomas, xanthelasms or corneal arcus, and a history of early CVD in the patient or close relatives, are important diagnostic factors of FH. These factors are used as medical criteria for the disease. In order to optimize the clinical and cost effectiveness of genetic testing services for FH, it is important to find the patients who most likely have genetic mutations. The Simon Broome criteria from the UK, the Dutch Lipid Clinic Network criteria from the Netherlands, and the MedPed criteria from the USA are the three main criteria used today (31). Molecular and genetic testing has contributed to considerably more precise diagnostics.

1.2.2 Prevalence and clinical manifestations

The frequency of FH was formerly reported as 1/500 individuals. However, several studies in recent years have suggested a higher frequency. Akioyamen et. al. published a meta-analysis in 2017 stating that the disease is thought to be affecting approximately 1/250 individuals worldwide (32). Faggiano et. al. further highlighted that the prevalence of FH is higher among patients with verified CHD compared to the normal population (33). The HoFH variant is uncommon, and the prevalence is estimated to be 1/160000 to 1/1000000 (15, 34).

Coronary atheroma, xanthelasma, premature corneal arcus, and achilles tendon xanthomas are often to be found in untreated FH-patients, and acts as strong indicators of long-term exposure to high LDL-C (35, 36). Over half of the untreated FH-patients will most likely have developed CVD by the age of 55, and most of them will die between 35 to 65 years (37).

Previous studies in Norwegian FH-patients suggest that women get their first cardiovascular (CV) event at the same age men (38), and that the average age of death is almost the same in the two sexes (39, 40).

1.2.3 Risk factors of cardiovascular disease

Many factors affect the risk of CVD, some of them are non-modifiable, while others can be changed. Table 1 shows an overview of the different risk factors, derived from The Cholesterol Charity – Heart UK (41). The presence of more than one risk factor leads to a greatly elevated risk of CVD, giving FH-patients a vast disadvantage because of the high cholesterol since birth. At the age of 45, FH-patients have gained an accumulated LDL-C exposure equivalent to a 70-year old healthy person (42). Akioyamen et. al. conducted a meta-analysis of the risk factors for CVD and found, in decreasing order of importance, that hypertension, family history, diabetes, elevated Lp(a), current smoking, male sex and low HDL-C significantly elevated the risk (43). Additionally, Millett et. al. found that hypertension, diabetes and smoking elevate the risk of CHD relatively more in women compared to men (44).

Table 1: Overview of risk factors of CVD

Non-modifiable	Modifiable
Age Gender Family history	High blood pressure High cholesterol Diabetes Smoking Overweigh/obesity Physical inactivity Unhealthy diet Excessive alcohol Excessive stress

Risk factors derived from the Cholesterol Charity – Heart UK (41).

Lifestyle factors

Hypertension is one of the strongest risk factors for CVD (45-47). Likewise, obesity and diabetes are strong risk factors of CVD by altering the pathways of the energy metabolism and increasing the metabolic stress (48). These factors combined contribute to the metabolic syndrome (MetS), which is one of the most important contributors to CVD and deaths worldwide (49, 50). In addition to obesity, diabetes and hypertension, MetS is also defined by raised triglyceride levels and low HDL-C levels (51). The National cholesterol Education Program Adult Treatment Program (NCEP ATP) III and the International Diabetes Federation (IDF) are two well-known diagnosis criteria for Mets (52, 53). For patients with MetS, a healthy lifestyle which includes a high intake of fiber, fruit and vegetables, as well as regular physical activity is important to prevent the development of CVD (54).

Smoking is also a major independent risk factor of CVD. Even minor exposures of tobacco smoking increases the risk of acute myocardial infarction (AMI) and the total mortality (55, 56). Yusuf et. al. proposed in the case-control study INTERHEART that the odds ratio of

getting a myocardial infarction were 2.27 for former smokers and 3.87 for current smokers compared to a non-smoker (57). Smoking cessation, or even smoking reduction, is associated with improved survival. A reduction of 5 cigarettes a day for patients who have experienced AMI gave an 18% reduction of mortality risk (58). In healthcare, smoking cessation is therefore one of the most prioritized lifestyle changes for an FH-patient.

High density lipoproteins (HDL)

The role of HDL cholesterol (HDL-C) in CVD development is currently under debate. HDL-C has been considered the «good type» of cholesterol for a long time. The Framingham study showed that low levels of HDL-C was associated with increased mortality (59), and Mahdy et. al. showed a reduction in cardiovascular risk by 2-3% with an increase of HDL-C of 0,259 mmol/L (60). It was proposed that HDL-C reduced the pathogenic activity of the LDL-C through reverse cholesterol transport. Acton et. al. also described other non-lipid related mechanisms of HDL which includes inhibition of monocyte adhesion and prevention of thrombosis (61). However, newer discoveries suggest that the level of HDL-C may rather act as a biomarker of lifestyle and behavior instead of being a causal factor of CVD. A large population-based study by Madsen et. al. concluded that an extremely high HDL-C level is associated with increased cardiovascular and all-cause death (62). According to Allard-Ratick et. al., the cardiovascular risk followed a U-shaped curve (63). An HDL-C level between 1.1-1.5 mmol/L was associated with the lowest risk of cardiovascular disease, whereas the risk was highest among those with HDL-C levels < 1.1 mmol/L and > 1.5mmol/L.

Lp(a)

Lipoprotein little a (Lp(a)) is synthesized in the liver and is an LDL-like particle with an apolipoprotein (a) (apo(a)) chain linked to the apoB-100 by a disulfide bond. High concentrations of Lp(a) is known as an independent risk factor for CVD, both by interfering with the fibrinolytic activities of plasminogen, and by enhancing atherosclerosis (64). As Lp(a) are small, dense and cholesterol-rich particles, they can easily penetrate the arterial lining and are susceptible to oxidative modifications. This make them pro-inflammatory and pro-atherogenic (65). The plasma concentration of Lp(a) varies among individuals and ethnicities, and is genetically determined (66). Statins and ezetimibe have not been able to reduce the levels of Lp(a), while PCSK9-inhibitors, niacin and LDL-apheresis have shown to reduce it (67). Patients with high LDL-C as caused by FH have further exaggerated risk for CVD if they also have high Lp(a) concentrations.

High-sensitivity C-reactive protein

The atherosclerotic process is accompanied by an on-going low grade systemic inflammation with activation of the immune system and inflammatory cytokines (68). Inflammatory cells accumulates inside the growing plaque, and the inflammation rate influences the stability of the plaque and the likelihood of rupture. C-reactive protein (CRP) is an acute phase protein produced in the hepatocytes as a response to cytokines, and is often used as a biomarker for inflammation. Upon evaluating CVD risk, high-sensitivity CRP (hsCRP) is used as biomarker, as this detects CRP levels as low as 0.1 mg/L. Patients with hsCRP levels <1, 1-3 or > 3 mg/L can be classified into low, intermediate and high risk of CVD, respectively (69). The Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (Prove IT – TIMI 22) study showed that statins could reduce both LDL-C and CRP levels. Patients with acute coronary syndromes who reached CRP levels < 2 mg/L had significantly better survival compared to those with higher CRP, regardless of LDL-C levels (70). Nissen et. al. showed that a reduced progression of atherosclerosis in patients with coronary artery disease (CAD) was associated with reduced LDL-C and CRP levels through statin treatment (71).

1.3 Medications and treatments

The aim of the treatments in FH is to lower the patients' CVD risk, in particular by reducing LDL-C levels to target. Lifestyle modifications and optimal dietary choices should always be established.

Dietary treatment

A heart-friendly diet is characterized by a limited intake of saturated fat, high intake of plant sterols and fiber, and limited use of sugary beverages and food. The DASH diet and the Mediterranean diet are both much like the heart –friendly diet, and are proved to be protective against CVD (72-74). Substitution of saturated fatty acids with unsaturated fatty acids reduces the risk of CVD by decreasing the LDL-C levels and enhancing the HDL-C levels (75-77). However, substitution of saturated fat with a higher carbohydrate intake, especially refined carbohydrate, may rather increase the risk of CVD through increasing obesity and insulin resistance, as well as elevated TG and lower HDL-C (78, 79). These dietary interventions have also shown to alter the composition of the LDL-C particle, making it more favorable. As

in the Healthy Nordic Diet, a higher intake of unsaturated fats decreases LDL-C aggregation, while a higher intake of sucrose and saturated fat increases aggregation (12).

Physical activity

The minimum recommended amount of physical activity for the general population in Norway is 150 minutes with moderate intensity, or 75 minutes with high intensity, per week, set by the Norwegian Directorate of Health (80). The The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines recommends regular physical activity for at least 30 minutes a day for people with FH (79). Physical activity have not been linked to any specific effects on total cholesterol (TC) or LDL-C reduction, but the benefits of exercise still applies to the other risk factors such as weight maintenance, hypertension, type 2 diabetes and other chronic diseases (79, 81).

Smoking cessation

Tobacco smoking is a strong risk factor of many diseases, including CVD. Smoking is associated with oxidative stress whereby endothelial dysfunction and hypertension is induced (82). Smoking cessation is therefore advised in order to decrease the risk of CVD, and is included in all guidelines for prevention of cardiovascular disease (79, 83).

Lipid lowering medications

Even though a healthy lifestyle with optimal diet is an important focus of treatment, FH-patients most often need additional drug treatment to reduce LDL-C to target due to the very high inborn LDL-C level. A number of medications are developed in order to lower the LDL-C levels, including HMG-CoA reductase inhibitors (statins), bile acid sequestrants (resins), nicotinic acid (niacin), fibric acid (fibrates), cholesterol absorption inhibitors (ezetimibe), and PCSK9-inhibitors. The ESC/EAS guidelines for management of dyslipidemias have stated that the first line treatment for patients with FH is high intensive statin therapy, with combined ezetimibe treatment in most cases (79). However, patients with extensively elevated LDL-C levels despite maximally tolerated statin therapy with ezetimibe treatment should be offered additional treatment with PCSK9-inhibitors (79, 84). As stated by the ESC/EAS Task Force in 2017, inhibition of the HMG-CoA reductase by statins, reduced cholesterol absorption from food by ezetimibe, and PCSK9 inhibition, will give an enhanced combined lipid lowering effect (84). Nordestegaard et. al. illustrate the positive benefits of early initiation of lipid lowering medication (LLM). They argue that detection and treatment

of FH-patients should start as early in life as possible in order to limit the total accumulated cholesterol burden as much as possible (85). They also mention that statin therapy can improve survival of CVD in FH-patients.

Atherosclerosis is a dynamic process where atherosclerotic plaques can either progress, stabilize or regress depending to their surrounding environments (86-89). A meta-analysis published in 2010 by The Cholesterol Treatment Trialists' Collaboration (CTT) stated that every 1 mmol/L reduction in LDL-C reduces the risk of CVD mortality and morbidity by 22% during 5 years, regardless of initial LDL-C levels (90). On basis of clinical trials, the ESC/EAS guidelines has set the treatment goals to LDL-C < 2.5 mmol/L for those in primary prevention, and < 1.8 mmol/L for those who have already experienced CVD or are in very high risk (VHR).

Side effects of the lipid lowering treatment

Statin therapy will greatly reduce the risk of CVD, and are generally thought to be well-tolerated (91). Even though statins intolerance is uncommon in randomized trials, statin associated symptoms are still frequently reported in clinical practice (92). Statin associated muscle symptoms (SAMS) are the most common side effect of statins, and were reported by 10% of the patients receiving statin therapy in the Prediction of Muscular Risk in Observational conditions (PRIMO) study (93). In the Understanding Statin Use in America and Gaps in Patient Education (USAGE) survey conducted in the US, 25% of the current statin users reported SAMS, and 62% stated that they discontinued statins because of side effects (94). When handling statin intolerance, it is recommended to either lower the statin dose, discontinue the statin and re-challenge it after a period of time, change the type of statin, or change to other LLM (91).

Ezetimibe acts by inhibiting intestinal uptake of dietary and biliary cholesterol, and is often used in combination with statin treatment. The statin-ezetimibe combination has a greater lipid-lowering effect compared to statin monotherapy, and is more effective in reducing CV events (95, 96). According to the ESC/EAS guidelines, ezetimibe is considered safe, and is recommended as second-line treatment in addition to statin therapy. There has not been reported any serious side effects of ezetimibe, and the most frequent side effects are elevated liver enzymes and muscle pain (79).

Resins are not absorbed when ingested, and act by binding to bile acids in the intestine, preventing the bile to enter the enterohepatic circulation. This in turn will upregulate the hepatic LDL-R activity, clearing LDL-C from the circulation. Common side effects of resins are mostly gastrointestinal (GI) effects and the bulkiness of the resins (79, 97). Former resins, cholestyramine and colestipol, have interactions with many commonly prescribed drugs, while colesevelam is better tolerated with less interactions and can be administered together with statins.

PCSK9-inhibitors, Alirocumab and Evolocumab, are novel treatment and are recommended by the ESC/EAS Task Force to patients in VHR and patients with high LDL-C levels in spite of maximal lipid lowering treatment (LLT) (84). The use of PCSK9-inhibitors on top of traditional treatment can reduce the LDL-C even further by up to 74% (98-102). A study by Sabatine et. al. tested the clinical outcomes of Evolocumab and reported a 15-20% reduction in CVD risk after 2 years (103). Another study, conducted in 2018, reported a lower risk of recurrent CVD among patients receiving Alirocumab (104). These studies also conclude that PCSK9-inhibitors are relatively safe to use with little to no adverse effects, with an exception of local reactions at the injection-site. However, it still remains to evaluate the long-term effects of these new drugs.

1.4 Knowledge gaps

The risk of cardiovascular disease increases with age, and can be strongly influenced by different factors in life. As defined by ESC/EAS guidelines, persons with FH are at particular high risk of CVD because of the LDL-C burden from birth (79). Early detection and start of treatment early in life is therefore crucial in preventing early development of atherosclerosis. Diet interventions may reduce the LDL-C levels by up to 10% on average, but diet alone is usually insufficient to substantially alter disease progression in most FH-patients (105).

Limited data exist regarding compliance to LLM and dietary advices among FH-patients in Norway. Though several reports have shown that undiagnosed and untreated FH-patients are at high risk of CVD, we do not know exactly the prognosis of the patients who no longer receive follow-up from specialized institutions. Among the assumed 25 000 persons with FH in Norway, only around 30% is genetically diagnosed today (106). How old were they when they first got their clinical FH diagnosis? How many patients initiated treatment too late? How many people are receiving high potent LLM? How many have reached their treatment

target? How well does this population follow the recommendations regarding physical activity and heart friendly diet? There are still questions on whether there are differences between various subgroups in this population. Additionally, it is important to investigate how many FH-patients have additional risk factors, qualifying them to the VHR group.

This master's thesis provides some data and aim to point out possible improvements of the treatment for FH-patients. A description of today's situation, together with a comparison to the past, can show a picture of how the patients have developed and incorporated the treatments in their life. This may potentially point out achievements, and also potential improvement areas for the Lipid Clinic.

2 Aims

The aim of this study is to study FH-patients in a long-term real life setting in a highly specialized lipid clinic. This paper will work as a quality assessment of the previous findings and analyses of the patients' lipid and blood parameters, treatment targets, medications and its side effects, dietary behavior and lifestyle. We are interested in revealing whether there have been any changes in these parameters between visit 1(V1) and visit 3 (V3). It is also of interest to compare different subgroups in the population.

2.1 Specific aims

- To present the use of LLM and its side effects
- To detect changes from V1 to V3 regarding
    a) Diet and lifestyle factors
    b) Clinical and biochemical measurements
- To investigate the development and prevalence of
    a) metabolic syndrome (MetS) in FH-patients during 8-12 years
    b) CVD during 8-12 years follow-up
- To identify differences in diet and lifestyle factors, and clinical and biochemical measurements between
    a) Those with and without MetS
    b) Those with CVD and healthy subjects
    c) Patients at the lipid clinic (LC) and those outside the LC
    d) Patients in high risk and very high risk of CVD
- To investigate gender differences in biochemical measurements and CVD development

3 Subjects and methods

3.1 Implementation of the study

The TTT-FH study started in 2006. During the period of January to July 2006, all FH-patients between the age of 18 to 75 were continuously invited to participate in the study during their routine visit at the LC (n=426). Verification of the disease were either by genetic testing or by the use of the Dutch Lipid Clinic Network (DLCN) criteria (85). Initially, the TTT-FH study was intended to be a quality assessment of the treatment given at the LC, thus an approval by the Regional Ethical Committee for Medical Research was not needed at the starting time.

Exclusion criteria were:

i. Participating in other on-going projects with unknown medications or interventions
ii. Receiving LDL apheresis
iii. Dropping out of scheduled consultations during the half year
iv. Not able to fill out questionnaires or join telephone interviews
v. Not willing to participate
vi. Serious concomitant disease e.g. malignant disease

3.1.2 The first visit, V1

A total of 357 out of 426 invited participated in the study. Figure 3 shows a summary of the included and excluded participants throughout the study. Fasting blood samples were drawn shortly prior or after the visit. Anthropometric measurements were acquired during the doctor's consultation for most patients, but some were self-reported at the telephone interviews. During the visit 1, information of the participants were conducted through three questionnaires; i) the doctor's form (appendix 1), ii) The SmartDiet (appendix 2) and iii) The patients' preference form (appendix 3).

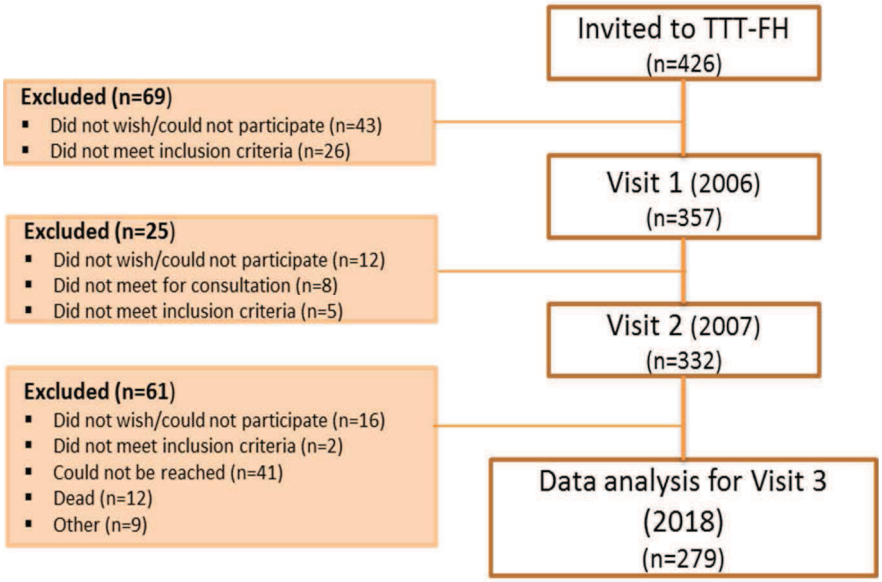

Figure 3: Flowchart of subject recruitments to the project.
Visit 3 consisted of 4 parts. This thesis summarizes the accumulated data for all patients of all parts.

3.1.3 The second visit, V2

Visit 2 (V2) was conducted about one year after V1, in 2007. All 357 participants were invited to a new consultation at the LC, in which 332 patients wished to continue in the study. Of those who were not included, 43 could not or did not wish to participate and 26 did not meet the inclusion criteria. The data was collected according to the same procedures as in V1 by Dr. Kjell-Erik Arnesen. The patients' preference form was not included during this visit.

3.1.4 Visit 3, Part I, II, III and IV

Three master's students recruited and analyzed a total of 216 patients for V3, part III from 2015 to 2017, supervised by Dr. Arnesen. Visit 3, part VI was conducted between June and December 2018, and was supervised by Dr. Arnesen and Dr. Retterstøl. The data analysis was carried out from January to May 2019. The different parts of V3 were conducted at different times, and each analysis were done with accumulated number of subjects. An overview of all parts are shown in table 2.

Table 2: Summary of Visit 3, Part I, II, III and IV

	Visit 3, Part I	Visit 3, Part II	Visit 3, Part III	Visit 3, Part IV
Author	M.T.	I.M.	K.R.	A.P.
No. invited	110	290	164	120
No. analyzed	64	156	216	279
Publishing time	may 2015	nov 2016	nov 2017	june 2019

M.T., Marlene Thorvall; I.M., Irene Mork; K.R., Karoline Randsborg; A.P., Ann Phung.
No. invited shows number of invited patients to each respective visit.
No. analyzed shows the accumulated number of participants in the study that was analyzed at the respective visits.

3.1.5 Recruitment and management of the participants in V3, part IV

During August and September 2018, invitation letters were sent to all the remaining 120 patients who had not attended V3. The participants who lived close to the city, but have not been followed up by the LC in a long time, were invited to a consultation. Other patients who recently have been at the LC, or who lived far away, were invited to a telephone interview. Fifteen patients were invited to a consultation at the LC, 5 were already on the waiting list for a consultation at the LC, and 95 patients got an invitation to a telephone interview. The patients who did not respond to the invitation letters, were attempted to be reached by phone on three different days. Those with unsuccessful contact were excluded from the study. A total of 14 consultations and 49 telephone interviews were completed between October –

December 2018. The total number of patients included in the analysis for V3 Part IV is 279. Figure 4 displays the timeline of the whole study.

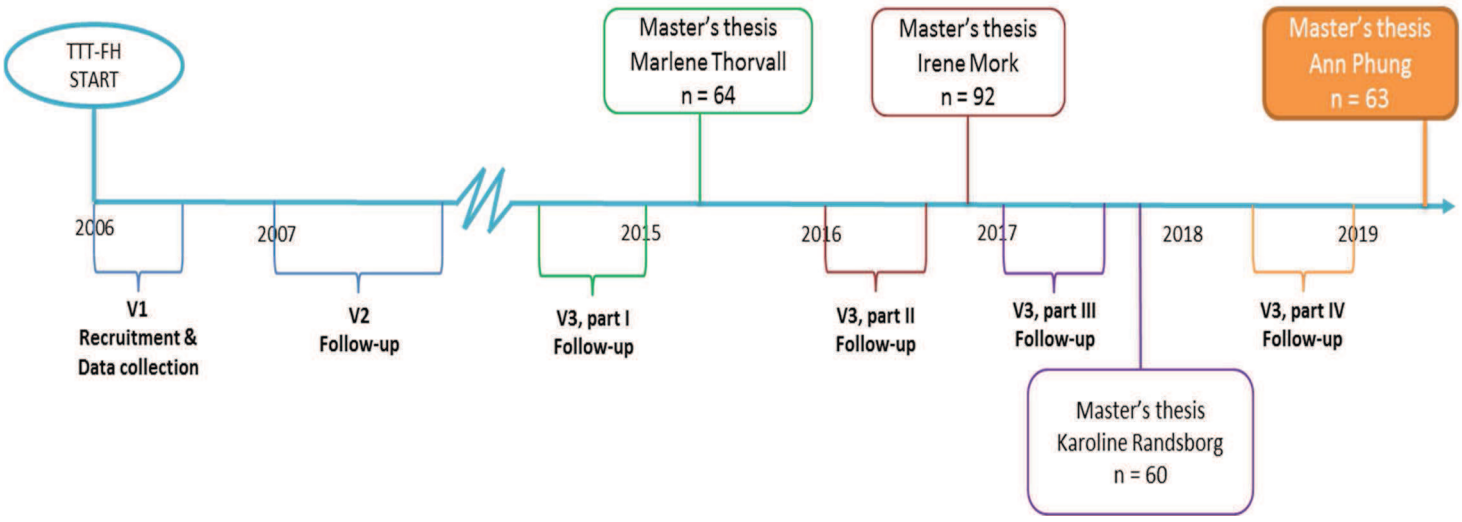

Figure 4: Timeline of the Treat-to-target Familial Hypercholesterolemia (TTT-FH) study.
Square bubbles show published master's thesis by the respective master's students, with number (n) of recruited participants done by each student.

3.2 Materials

3.2.1 Data collection

The data at V3 Part IV was collected using the same procedure as in V1. The patients had to fill out three forms together with the doctor and/or the master's student. The consultations were held by Dr. Kjetil Retterstøl at the LC, where the patients got a thorough examination of their health and medical state, before getting a review of their diet and lifestyle with the master's student. The patients had blood samples analyzed for the routine biological analyses at the LC. Records of CV events were retrieved from the patients' journals.

The doctor's form

During the interview and the doctor's consultation, a doctor's form (appendix 1) was filled out in order to acquire the patients' current medication regimen, the patients' social state and potential endpoints (CVD). The form was developed in 2006 for this project. It also included adverse effects from the treatment, as well as changes in the treatment regimen over the years with an explanation of why the changes were made. The adverse side effects were categorized based on the affected organ systems, shown in table 3. The effects were further classified according to the likelihood of whether the effects are caused by the LLM:

- Definite: if the effect disappeared after termination of the medication, and reoccurred at initiation of the same medication. Both the doctor and the patient got a definite impression of the adverse effect by retesting the treatment several times over the years.

- Probable: if the impression of the adverse effect is somewhat less certain than definite.

- Possible: doubtful relation between the adverse effect and the LLM

With the patients' permission, missing information was obtained from the patients' medical journals to the furthest extent.

Table 3: Classification of possible side effects from lipid lowering medications.

Gastrointestinal	Muscle	Neurological	Psychological	Sexual problems	General/other
Flatulence	Muscle pain	Headache	Anxiety	Impotence	Malaise
Diarrhea	Muscle stiffness	Wilt	Nervousness		Dyssomnia
Constipation	Muscular asthenia	Numbness	Depression		
Abdominal pain					

The side effects were self-reported and collected from the doctor's form.

The SmartDiet

The SmartDiet form (SmD) (appendix 2) is a questionnaire developed by the Lipid Clinic for evaluating the patient's diet according to the heart-friendly diet recommendations (107). The form has been revised several times in order to be updated according to the improved availability of different products. To be able to compare the results from V1 to V3, the old version from 2003 was utilized to the furthest extent.

The SmD from 2003 consists of 15 questions with three alternatives. Each alternative corresponds to either 1, 2 or 3 points. If the patient chooses more than one alternative, the mean score of that question is used. The total score of the form can then be categorized into low, middle or high score. A total of 29 points or less is defined as "a low score" with "potential for improvement in several areas". A score between 30 and 37 corresponds to the middle category with "potential for improvement on some areas". A total score of 38 points or higher indicates that the patient has "healthy dietary habits".

The last part of SmD consists of questions about lifestyle. This part is being used in combination with the part regarding lifestyle in the Doctor's form. Anthropometric data, such as height, sex, weight and whether the patient desires to lose weight, is gathered here.

Biological analyses and anthropometric data

The patients received a prefilled requisition form for blood samples together with the invitation to participate in the study. The patients could then bring the requisition form to their regular laboratory or general practitioner (GP) in order to draw fasting blood samples. If there were noteworthy or concerning results, the master's student consulted the doctor before giving feedback to the patient. The blood analyses included lipid values, fasting glucose, HbA1c and CRP among others. Lp(a) was measured at different times throughout the patients' lives, and not all had available values at V3. Hence, the highest or only value was retrieved from their journals and used in this master's thesis. The student manually calculated values for non-HDL-C and ApoB/ApoA1 ratio. The patients' first measured TC and LDL-C values were also retrieved from their medical journals.

The patient's preference form

The patient's preference form consisted of two pages and included questions about the patient's follow-up routine for their FH (appendix 3). The form's objection was to explore the patients' satisfactory level with the health care and the follow-up they were offered, as well as their trust in medications, side effects and the importance of low cholesterol levels. The master's student filled out the questionnaire during the interview with the patients. The patients who met to consultation filled out the form prior to their appointment, before discussing it with the master's student later.

3.2.2 Statistical analysis

All statistical analyses were carried out using IBM SPSS Statistics version 25.0 (SPSS Inc, Chicago). In order to reduce the risk of plotting errors, all variables of randomly selected patients were frequently double-checked. Missing data was given a blank cell in SPSS. To keep the samples size as large as possible, pairwise exclusion of cases was chosen instead of listwise when encountering missing values. The number of patients will be listed as "n=" for each variable if the analyzed population differed from the originally 279 participants.

Continuous variables were checked for normal distribution using histograms, box-plots, normal Q-Q plot and mean to median ratio. Continuous variables with normality were

presented with the mean and 95% confidence interval (95% CI), while skewed variables were presented with median and 25^{th} – 75^{th} percentiles (25-75p) or minimum and maximum values (min-max). Categorical variables were portrayed as number of cases and percentages of the total number of cases.

Student's t-test, either independent or paired, were used when comparing two normally distributed continuous variables. In the case of skewed variables, Mann-Whitney U test or Wilcoxon signed rank test was performed. Differences between categorical variables were tested using Chi square test for independence, or Fisher's exact test if the assumptions for using Chi-scare test were violated. For paired sample test with categorical values, McNemars test was used. A p-value < 0.05 was considered statistically significant. Analysis of variance (ANOVA) was used to test for statistical significance for three or more groups. Further testing between each sub-groups was carried out only when the ANOVA testing gave significant results. Stratification was used as the main method to adjust for factors like sex or types of treatment. When many independent factors were tested, Bonferroni correction was used to control for multiple comparison. Accordingly, when there were variables that were dependent, for example different cholesterol particles, false discovery rate (FDR) was used to correct for multiple testing (108). However, this thesis is mainly a descriptive analysis with explorative p-values, hence regression statistics or advanced analyses were not conducted.

When outliers or extreme values were detected, the tests were performed both with and without these values. If removal of these values affected the significance of the results, this was noted either in the tables or the test.

SmartDiet

The questions from SmD were classified into four categories, where the points of each questions were summarized. Table 4 shows a summary of the categories. One of the differences between the 2003-version and the newer versions, was that questions 12 and 13 about fruits and vegetables intake were merged as one question in the newer versions. To be able to compare the results from the different versions, question 12 and 13 from the 2003-version were merged to one category with a maximum score of three points. A summarized score for question 12 and 13 in the 2003-

Table 4: Overview of the analyzed SmartDiet food categories.

Category	No. Of questions	Maximum score
Diary	4	12
Meat	2	6
Fish	2	6
Fruit and vegetable	1	3

version of 2 points, 3-4 points and 5-6 points, corresponds to 1, 2 and 3 points in the newer versions, respectively.

High-risk patients, co-morbidities and metabolic syndrome

Very high individual risk score is defined as a 10-year risk of fatal CVD over 10% using the European high risk chart – SCORE (109). This chart evaluates the risk based on gender, age, blood pressure, total cholesterol and smoking status. However, those who have been untreated until the age of 40 years have further increased risk for CVD (85, 110, 111). This factor is included in the New French Society of Atherosclerosis's (NSFA) definition of FH-patients in VHR. This thesis will therefore use both the definition from ESC/EAS and NSFA to classify the risk profiles of FH-patients. An overview of the criteria is shown in table 5.

Table 5: Overview of the criteria for patients in very high risk

ESC guidelines' definition
Individual SCORE-risk > 10% (all 3 criteria underneath must be fulfilled)
Systolic blood pressure > 140 mmHg for men and >160 mmHg for women
Age > 50 years for men and >55 years for women
Total cholesterol >4mmol/L
Smoking
Documented CVD, diabetes or chronic kidney disease
Additional criteria in the NSFA definition
Untreated before the age of 40 years

At least one of the listed criteria must apply to define patients in very high risk.

The co-morbidities included in this thesis are diabetes and hypertension. A patient is considered to have diabetes if he/she is receiving diabetes treatment. Likewise, hypertension is defined by the use of hypertension treatment. Measured HbA1c and blood pressure at V3 are not used as definite diagnosing criteria, as they may be a causal findings that need to be controlled prior to any decision of diagnosis.

The diagnosis of MetS was based on the criteria from NCEP/ATP III, which is also used by the Norwegian Directorate of Health (80). Since some of the variables do not have a complete dataset, more variables were used to define one criteria. For the criteria regarding waist circumference, both measured waist circumference and BMI>30 were used to define this criteria, and the patient only needed to fulfill one of them. As for blood pressure, both measured blood pressure and hypertension treatment were used. Likewise for fasting plasma-glucose, glucose > 5.6mmol/L, HbA1c >6.5% and diabetes treatment were used to define that criteria. It is important to investigate the role of MetS in FH-patients, as it further increases the risk of CVD (112-114).

4 Results

4.1 Description of the study population at V3

4.1.1 Population characterization

The clinical characterizations of the study population at V3 are summarized in table 6. 53.4% of the population was male, and the majority had genetically verified FH. The mean age of first known high TC was 27.9 years. Only 30% of the patients were aware of their hypercholesterolemia before the age of 20 (data not shown). All participants have been patients at the LC in Oslo for several years before V1. Most patients were still followed up by the LC at V3. Other hospitals and the GP were also used as follow-up, but mainly among those who lived outside of Oslo, or had stable lipid values and were discharged by the LC. Of the patients untreated before the age of 40, 60.3% were female. 18 patients did not use LLM, of whom 5 were male. A characterization of the patients without LLM is presented in section 4.1.4.

The mean BMI in the population corresponded to "overweight", and were similar between male and female. Over 1/5 of the population is categorized as obese. 10% of the whole population received diabetes treatment, and a larger proportion were males. Diabetes, defined by the use of diabetes treatment, was present among 13% of those who received high intensity statin therapy, while only 2% of those with moderate intensity had diabetes (data not shown). Diabetes was also more prevalent among those over 50 years compared to those under 50 year (13.9% vs 3%, $p=0.004$). 28% of all patients received hypertensive treatment and are defined as having hypertension (table 6). Only 3% of those under 50 years had hypertension, while 41.7% over 50 years had hypertension ($p<0.001$). 4.2% of the participants at V3 had systolic and diastolic values measured above 140/90 mm Hg (data not shown).

73.8% of the patients used high intensity statin therapy (table 6). The combination of statin and ezetimibe was the most used form, and was used by 48.7% of the population (97.1% of those with double medication). During the study period, 25 patients initiated PCSK9-inhibitor treatment. An overview of the side effects is presented in table 7. 34% of those who used LLM experienced side effects. 31.3% of the statin users experienced side effects, but only a smaller portion was categorized as "definite". Colesevelam was the second LLM after statins

that gave most side effects, and affected 27.3% of its users. The side effects were mostly associated with muscle pain for statins, and GI problems for colesevelam.

Table 6: Clinical characteristics at V3 in the total population, the females and males, those who were untreated before 40 years and those without lipid lowering medication.

	Total (n=279)		**Male (n=149)**		**Female (n=130)**		**Untreated before 40 years (n=68)**		**Patients w/o medication (n=18)**	
	mean	**(95% CI)**	**mean**	**(95% CI)**	**mean**	**(95% CI)**	**mean**	**(95% CI)**	**mean**	**(95% CI)**
Age (years)	55.2	(53.6, 56.6)	55.0	(52.8, 57.1)	55.4	(53.0, 57.8)	66.4	(63.5, 69,3)	49.4	(42.1, 56.8)
BMI (kg/m^2)	27.1	(26.5, 27.7)	27.3	(26.6, 27)	27.7	(25.9, 29.5)	28.3	(25.1, 31.6)	25.4	(23.5, 27.3)
Co-morbidity	n (% of total)		n (% of males)		n (% of females)		n (% of untreated)		n (% of no LLM)	
Diabetes	28	(10%)	20	(13.4%)	8	(6.2%)	5	(7.4%)	0	(0.0%)
Hypertension	78	(28%)	44	(29.5%)	34	(26.2%)	33	(51.6%)	3	(16.7%)
Obesity	63	(22.6%)	35	(23.5%)	28	(21.5%)	13	(19.1%)	2	(11.1%)
Very high risk patients[a]	159	(57%)	81	(54.4%)	78	(60%)	68	(100%)	5	(27.8%)
Type of FH diagnosis										
Genetically verified FH	241	(86.4%)	131	(87.9%)	110	(84.6%)	50	(73.5%)	14	(77.8%)
Clinical definite	17	(6.1%)	9	(6%)	8	(6.2%)	6	(8.8%)	3	(16.7%)
Clinical probable	14	(5%)	6	(4%)	8	(6.2%)	10	(14.7%)	1	(5.6%)
Clinical possible	7	(2.5%)	3	(2%)	4	(3.1%)	2	(2.9%)	0	
LLM										
High intensity statin therapy[b]	206	(73.8%)	127	(85.2%)	79	(60.8%)	44	(64.7%)		-
Moderate intensity statin therapy[c]	50	(17.9%)	13	(8.7%)	35	(26.9%)	21	(30.9%)		-
Single medication	48	(17.2%)	20	(13.4%)	28	(21.5%)	17	(25%)		-
Statins[d]	43	(15.4%)	19	(12.8%)	24	(18.5%)	16	(23.5%)		-
Ezetimibe[d]	3	(1.1%)	1	(0.7%)	2	(1.5%)	1	(1.5%)		-
Colesevelam[d]	1	(0.4%)	0	(0.0%)	1	(0.8%)	0	(0.0%)		-
Double medication	140	(50.1%)	69	(46.3%)	71	(54.6%)	35	(51.5%)		-
Statin + ezetimibe[d]	136	(48.7%)	65	(43.6%)	71	54.6%)	32	(47.1%)		-
Triple medication	65	(46.3%)	46	(30.9%)	19	(14.6%)	14	(20.9%)		-
Statin + ezetimibe + colesevelam[d]	48	(17.2%)	35	(12.9%)	13	(4.7%)	8	(2.9%)		
Statin + ezetimibe + PCSK9[d]	13	(4.7%)	7	(4.7%)	6	(4.6%)	5	(7.4%)		-
Quadruple medication	9	(3.2%)	9	(6%)	0	(0.0%)	1	(1.5%)		-
Follow-up										
Follow-up at Lk	224	(80.3%)	119	(79.8%)	105	(80.8%)	42	(61.8%)	13	(72.2%)
Follow-up hospitals	14	(5%)	7	(4.7%)	7	(5.4%)	6	(8.8%)	0	(0.0%)
Follow-up PG	33	(11.8%)	17	(11.4%)	16	(12.3%)	17	(25%)	1	(5.6%)
No follow-up	8	(2.9%)	6	(4%)	2	(1.5%)	3	(4.4%)	4	(22.2%)

[a]Using the NSFA's definition.
[b]High statin therapy is defined as: atorvastatin (lipitor) 40-80mg or rosuvastatin (crestor) 20-40mg
[c]Moderat statin therapy is defined as: atorvastatin 10-20mg, rosuvastatin 5-10mg, pravastatin 40-80mg, simvastatin 20-40mg, lovastatin 40mg, fluvastatin 40mg, pitvastatin 2-4mg.
[d]Shown in number of users and % of the whole population in the respective groups (e.g total males and females).

Table 7: Medication use and side effects of lipid lowering medications at V3

	Users		Side effects, (%) of the number of users of each drug			
			Definite		Probable/possible	Definite/probable/possible
	n	(%)*	n	(% of users)	n (% of users)	n (% of users)
Statins	255	(91.4%)	20	(7.8%)	59 (23.1%)	79 (31%)
Colesevelam	55	(19.7%)	4	(7.5%)	11 (20.8%)	15 (27.3%)
Ezetimibe	209	(74.9%)	3	(1.4%)	7 (3.3%)	10 (4.8%)
Other	26	(9.3%)	1	(3.4%)	3 (10.3%)	4 (15.4%)

*Data shown in "n" number of patients and % of total population. Type of medication refers to all users of the medication in any dose and any combination. Drug use and side effects were retrieved from the patient's journals and self-reported usage in the doctor's form.

4.1.2 Blood parameters

The mean (95%CI) first known serum TC level was 9.8 mmol/L (9.5, 10.1), and was measured at a mean age of 27.9 years (n=272, data not shown). The mean first known LDL-C value was registered for 135 participants and was 7.4 mmol/L (7.1, 7.8). Lipid values at V3 are presented in table 8 and 9. There were statistically significant differences in TC, LDL-C, non-HDL-C, Lp(a) and ApoB between the patients with and without PCSK9-inhibitor treatment (table 8). The males were closer to the treatment goal in primary prevention of LDL-C<2.5 mmol/L at V3 compared to women, and the difference is statistically significant (table 9). To test whether the high mean TC and LDL-C of women were due to medication free periods, subjects without LLM were excluded from the analysis, and the differences were still statistically significant. The TC and LDL-C were 4.43 (4.3, 4.6) and 2.7 (2.5, 2.8) mmol/L for men, and 5.1 (4.9, 5.3) and 3.1 (2.9, 3.2) mmol/L for women, respectively.

Table 8: Presentation of clinical and biochemical measurements of total population, those on traditional medications and those with PCSK9-inhibitor add-on at V3.

	Total			Traditional treatment (n=255)			PCSK9 add-on (n=25)			*P**
	n	Mean	(95% CI)	n	Mean	(95% CI)	n	Mean	(95% CI)	
Total-C, *mmol/L*	273	4.9	(4.7, 5.1)	252	5.0	(4.8, 5.2)	21	3.9	(3.3, 4.5)	**0.002**
HDL-C, *mmol/L*	272	1.4	(1.3, 1.4)	252	1.4	(1.3, 1.4)	20	1.5	(1.3, 1.7)	0.261
LDL-C, *mmol/L*	273	3.0	(2.9, 3.2)	252	3.1	(2.9, 3.3)	21	2.0	(1.4, 2.6)	**<0.001**
TG, *mmol/L*	271	1.2	(1.1, 1.2)	251	1.2	(1.1, 1.2)	20	1.1	(0.9, 1.3)	0.595
Non-HDL-C, *mmol/L*	272	3.5	(3.3, 3.6)	251	3.6	(3.4, 3.7)	21	2.2	(1.6, 2.8)	**<0.001**
Lp(a) *mg/L*	242	562.2	(478.1, 646.3)	218	527.6	(442.5, 612.7)	21	988.8	(595.1, 1382.5)	**0.004**
ApoA1 *g/L*	260	1.5	(1.4, 1.5)	245	1.5	(1.4, 1.5)	15	1.5	(1.4, 1.7)	0.578
ApoB, *g/L*	262	1.1	(1.0, 1.1)	246	1.1	(1, 1.1)	16	0.8	(0.7, 1)	**0.004**
ApoB/ApoA1 ratio	260	0.74	(0.71, 0.78)	245	0.76	(0.72, 0.79)	15	0.54	(0.42, 0.67)	**0.003**
Glucose, *mmol/L*	235	5.5	(5.3, 5.7)	221	5.5	(5.3, 5.7)	14	5.5	(5.1, 5.8)	0.786
HbA1c, %	238	5.7	(5.6, 5.8)	226	5.7	(5.6, 5.8)	12	5.4	(5.2, 5.6)	0.203
Systolic BP, *mmHG*	214	129	(127, 130)	197	129	(127, 130)	17	129	(123, 134)	0.952
Diastolic BP, *mmHG*	214	77	(76, 79)	197	77	(76, 78)	17	81	(76, 85)	0.101

*P <0.05 is considered statistically significant differences between the group with traditional treatment and those with PCSK9-inhibitor add-on, tested with Independent samples T-test. Significant values in bold. Corrected for multiple testing using False Discovery Rate.

Table 9: Presentation of clinical and biochemical measurements of those untreated before 40 years, males and females at V3.

	Untreated before 40 years (N = 68)			Male (N = 149)			Female (N = 130)			*P**
	n	Mean	(95% CI)	n	Mean	(95% CI)	n	Mean	(95% CI)	
Total-C, *mmol/L*	66	4.9	(4.5, 5.2)	144	4.5	(4.3, 4.8)	129	5.3	(5.1, 5.6)	**<0.001**
HDL-C, *mmol/L*	66	1.5	(1.4, 1.6)	144	1.3	(1.2, 1.3)	128	1.5	(1.5, 1.6)	**<0.001**
LDL-C, *mmol/L*	66	2.9	(2.6, 3.2)	144	2.8	(2.6, 3.0)	129	3.3	(3.0, 3.5)	**0.004**
TG, *mmol/L*	66	1.3	(1.2, 1.4)	144	1.2	(1.1, 1.3)	127	1.2	(1.1, 1.3)	0.742
Non-HDL-C, *mmol/L*	66	3.3	(3.0, 3.6)	144	3.3	(3.0, 3.5)	128	3.7	(3.5, 4)	**0.006**
Lp(a) *mg/L*	57	730.7	(472.6, 988.8)	126	591.3	(478.0, 704.7)	113	534.1	(405.1, 663.1)	0.598
ApoA1 *g/L*	63	1.6	(1.5, 1.6)	133	1.4	(1.3, 1.4)	127	1.6	(1.5, 1.6)	**<0.001**
ApoB, *g/L*	64	1.0	(0.95, 1.1)	135	1.0	(0.97, 1.1)	127	1.1	(1.0, 1.2)	0.071
ApoB/ApoA1 ratio	63	0.70	(0.6, 0.7)	133	0.76	(0.71, 0.8)	127	0.73	(0.68, 0.78)	0.298
Glucose, *mmol/L*	55	5.8	(5.4, 6.3)	119	5.7	(5.4, 5.9)	116	5.4	(5.1, 5.7)	0.243
HbA1c, %	59	5.7	(5.6, 5.8)	123	5.8	(5.6, 6.0)	115	5.6	(5.5, 5.7)	**0.031**
Systolic BP, *mmHg*	43	131	(126, 136)	116	131	(128, 133)	98	126	(124, 129)	**0.016**
Diastolic BP, *mmHg*	43	78	(75, 81)	116	79	(78.2, 81.1)	98	75	(73.6, 76.9)	**<0.001**

*P <0.05 is considered statistically significant differences between male and female, tested with Independent samples T-test. Significant values in bold. Corrected for multiple testing using False Discovery Rate.

Of those untreated before 40 years, 60.3% were female and 33.3% reached LDL-C < 2.5 mmol/L. 53% had experienced a CV event, compared to 23.7% of those who were treated earlier than 40 years (p<0.001). Of the total population, 59.9% were in primary prevention at V3. The proportion of those who reached treatment targets of LDL-C < 2.5 and <1.8 mmol/L is presented in table 10. When excluding the PCSK9 users, 25.8% and 10.8% in primary and secondary prevention reached their treatment goals, respectively. Half of those with PCSK9-inhibitor add-on reached LDL-C < 1.8 mmol/L.

Table 10: Proportions of those who reached treatment targets at V3.

	Reached LDL-C target < 2.5 mmol/L	Reached LDL-C target < 1.8 mmol/L
Primary prevention (n=167)	44 (26.5%)	9 (5.4%)
Secondary prevention (n=112)	50 (44.6%)	13 (12%)
High intensity statin therapy (n=206)	85 (41.3%)	18 (8.7%)
Moderate intensity statin therapy (n=50)	9 (18%)	4 (8%)

Data presented in n and % of n in each respective group (e.g. primary prevention).

4.1.3 Diet and lifestyle factors

The majority of the population corresponded to the middle SmD category with "potential for improvement on some areas". Mean SmD score was similar in all four subgroups presented in

table 11. Only 5% of the population were in the lowest category, which corresponded to a self-reported unhealthy diet. Over half of the population was physically active ≥ 3 times per week, and the majority had an alcohol intake between 0-7 units per week. Generally, the population achieved high scores on meat and dairy. The mean score of fruits and vegetables corresponds to an intake of maximum 4 units per day, which is lower than the national recommendations, and can be improved even further.

Table 11: Dietary and lifestyle characteristics of the total population and different subgroups at V3.

	Total (n=279)	**Untreated before 40 years (n=68)**	**Patients without medication (n=18)**	**Male (n=149)**	**Female (n=130)**	***P****
	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)	
SmD Score	35.8 (35.4, 36.2)	35.8 (34.9, 36.7)	35.2 (33.4, 37)	35.7 (35.1, 36.4)	35.9 (35.3, 36.4)	0.954
Dairy	9.7 (9.5, 9.9)	9.2 (8.8,9.7)	9.4 (8.5,10.3)	9.9 (9.6,10.2)	9.4 (9,2,9.7)	**0.002**
Meat	5.5 (5.5, 5.6)	5.5 (5.3,5.7)	5.6 (5.3,5.9)	5.4 (5.3,5.6)	5.7 (5.6,5.8)	**0.040**
Fish	3.9 (3.8, 4.1)	4.3 (4,4.5)	3.8 (3.2,4.4)	4.0 (3.8,4.2)	3.9 (3.7,4.1)	0.732
Fruits and vegetables	2.1 (2.1, 2.2)	2.2 (2.1,2.4)	2.1 (1.8,2.3)	2.1 (2,2.2)	2.2 (2.1,2.3)	**0.033**
	n (% of total)	n (% of untreated)	n (% of no medication)	n (% of males)	n (% of females)	
SmD category 1	13 (4.7%)	5 (7.4%)	1 (5.6%)	10 (7.1%)	3 (2.3%)	0.094
SmD category 2	147 (52.7%)	34 (50%)	11 (61.1%)	76 (51.0%)	81 (62.3%)	0.070
SmD category 3	92 (33%)	24 (35.3%)	3 (16.7%)	51 (36.4%)	41 (31.5%)	0.702
Current smokers	38 (13.6%)	7 (10.4%)	1 (5.6%)	18 (12.1%)	20 (15.4%)	0.484
Former smokers	109 (39.1%)	30 (45%)	7 (38.9%)	56 (37.6%)	53 (40.8%)	0.797
Alcohol intake[a]						
Never	28 (10%)	5 (7.4%)	2 (11.1%)	13 (8.7%)	15 (11.5%)	0.550
<1 units	53 (19%)	8 (11.8%)	5 (27.8%)	22 (14.8%)	31 (23.8%)	0.066
1-7 units	116 (41.6%)	23 (33.8%)	5 (27.8%)	62 (41.6%)	54 (41.5%)	1.000
≥8 units	16 (7.5%)	6 (8.8%)	1 (6.5%)	15 (10.1%)	1 (0.8%)	**0.001**
Physical activity[b]						
Never	16 (5.7%)	3 (4.4%)	2 (11.1%)	10 (6.7%)	6 (4.6%)	0.607
<1 time/week	39 (14%)	6 (8.8%)	3 (16.7%)	25 (16.8%)	14 (10.8%)	0.169
1-2 times/week	72 (25.8%)	19 (27.9%)	6 (33.3%)	32 (21.5%)	40 (30.8%)	0.099
over 3 times/week	148 (53%)	40 (58.8%)	7 (38.9%)	79 (53%)	69 (53%)	1.000

*P <0.05 is considered statistically significant differences between men and women, tested with Mann-Whitney U-test, Chi-square test or Fisher's exact test. Significant values in bold.

[a] One unit is defined as 125 mL wine, 330 mL beer or 4 cL spirits.

[b] Number of sessions á 30 minutes with minimum moderate intensity.

SmartDiet; SmD.

SmD category 1 (<28 p) = poor diet, SmD category 2 (29-37 p) = should be improved, SmD category 3 (>38 p)= very good.

Max score dairy = 12p, max score meat and fish = 6p, max score fruits and vegetables = 3p.

4.1.4 The patients without statins or other lipid lowering medication

Twenty-three patients (women = 89%) were off statin treatment at V3 (table 12). Reasons for this were side effects (n=10), unwillingness towards statins (n=3), some were non-compliant without any given reasons (n=6) and some had an active wish for childbirth (n=4). The patients who were unwilling to use statins were convinced that they could be treated well

enough with only diet or herbal drugs. Patients with the wish for childbirth wanted to wait with medication initiation until childbirth was no longer relevant. The medications that were used instead of statins were ezetimibe (n=5), colesevelam (n=2) and PCSK9-inhibitor (n=1). Of these 23 patients, 18 did not use any lipid lowering medication at all.

Table 12: Characteristics and biochemical measurements of patients on and off statins.

	Patients with no medication (n=18)		**Patients off statins (n=23)**		**Patients on statins (n=256)**		***P****
	n	(%)	n	(%)	n	(%)	
Women	13	(72.2%)	16	(69.6%)	114	(44.5%)	**0.028**
Secondary prevention	3	(16.7%)	5	(21.7%)	104	(40.6%)	0.260
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	
Age at V3, *years*	18	48.3 (40.8, 55.9)	23	49.0 (42.1, 55.8)	256	55.7 (54.2, 57.3)	**0.017**
BMI, kg/m^2	18	25.4 (23.5, 27.3)	23	25.9 (23.6, 28.1)	255	27.2 (26.6, 27.9)	0.229
First measured Total-C, *mmol/L*	18	9.4 (8.4, 10.5)	23	9.6 (8.7, 10.6)	249	9.8 (9.5, 10.1)	0.681
First measured LDL-C, *mmol/L*	12	6.6 (5.3, 7.9)	14	6.9 (5.6, 8.3)	121	7.5 (7.1, 7.9)	0.361
Lipids at V3							
Total-C, *mmol/L* *	17	7.6 (6.4, 8.7)	22	7.5 (6.5, 8.5)	251	4.7 (4.5, 4.8)	**<0.001**
HDL-C, *mmol/L*	17	1.4 (1.2, 1.6)	22	1.5 (1.3, 1.7)	250	1.4 (1.3, 1.4)	0.312
LDL-C, *mmol/L* *	17	5.6 (4.6, 6.6)	22	5.6 (4.7, 6.4)	251	2.8 (2.7, 2.9)	**<0.001**
TG, *mmol/L**	17	1,0 (0.8, 1.2)	22	0.9 (0.8, 1.1)	249	1.2 (1.1, 1.3)	**0.022**
Non-HDL-C, *mmol/L**	17	6.2 (5.1, 7.2)	22	6.0 (5.1, 6.9)	250	3.3 (3.1, 3.4)	**<0.001**
Lp(a), *mg/L*	15	360.1 (141.5, 578.6)	20	376.7 (203.3, 550.1)	219	581.4 (490.2, 672.5)	0.189
ApoA1 *g/L*	16	1.4 (1.3, 1.6)	20	1.5 (1.3, 1.6)	240	1.4 (1.4, 1.5)	0.706
ApoB, *g/L**	16	1.6 (1.4, 1.8)	21	1.6 (1.4, 1.8)	241	1.0 (0.98, 1.0)	**<0.001**
ApoB/ApoA1 ratio*	16	1.2 (1, 1.3)	20	1.12 (0.98, 1.27)	240	0.71 (0.68, 0.74)	**<0.001**
Glucose, *mmol/L*	14	5.1 (4.7, 5.5)	17	5.2 (5.8, 5.6)	217	5.6 (5.4, 5.7)	0.254
HbA1c, % *	15	5.3 (5.1, 5.4)	18	5.2 (5.1, 5.4)	220	5.7 (5.6, 5.8)	**0.008**
Systolic BP, *mmHG*	10	121 (115, 127)	13	121 (116, 126)	200	129 (127, 131)	**0.029**
Diastolic BP, *mmHG*	10	74 (68, 79)	13	76 (71, 82)	200	78 (77, 79)	0.063

*P <0.05 is considered statistically significant differences between those on statins (n=256) vs those off statins (n=23), tested with Independent samples T-test, Mann-Whitney U-test and Chi square test or Fisher's exact test. Significant values in bold. Corrected for multiple testing using False Discovery Rate.

Of the 23 patients without statins, 2 had MetS at V3 and 5 had experienced CVD during the study period. With an average age of 49 years, those without statin therapy were 6.7 years younger than those who received statins, the difference was significant. Those with statin therapy became aware of their high cholesterol at mean age 29.6 years, while those without statins were 22.3 years, however the difference is not significant. Co-medication was used by 7 of the patients without statin therapy, and were mainly anti-hypertensive medications. The patients' lipid profiles at V3 are shown in table 13.

4.1.5 The patients' preferences concerning treatment and lifestyle

Figure 5 shows the answer distributions of the three statements regarding 1) the importance of a healthy lifestyle compared to medication treatment, 2) their treatment cholesterol values versus side effects and 3) their desire to acquire low LDL-C. The answer distribution at V3 were similar to V1, with an exception of the question about side effects. The proportion of those who think that little/no side effects is more important than low LDL-C increased from V1 to V3 (data not shown).

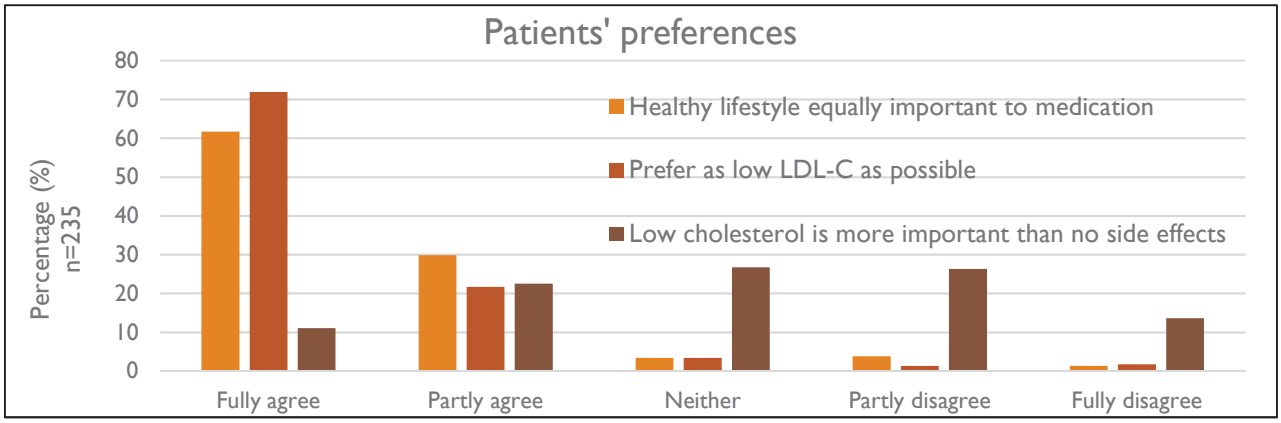

Figure 5: Answer distribution regarding patients' preferences.
Data was collected from the patient preference form and are shown as % of total answers in each agreement statement.

4.2 Differences between visits and subgroups

4.2.1 Changes from visit 1 to visit 3

Clinical differences in lipid profiles

Table 13 shows an overview of the lipid values from V1 and V3. Some significant moderate improvements were observed for LDL-C, non-HDL-C and total-C, while values of the variables regarding glucose tolerance and TG had a significant increase. Excluding the patients who used PCSK9-inhibitors from this analysis, there were still significant differences in TC, LDL-C, TG, non-HDL-C, ApoA1, glucose and HbA1c (data not shown). At V1, only 4.3% reached their treatment targets, while 20.4% reached their targets at V3. Mean untreated TC and LDL-C levels were 9.8 (9.5, 10.1) and 7.4 (7.1, 7.8) mmol/L, respectively.

Table 13: Clinical and biochemical measurements at V1 and V3.

		V1		V3		*P**
	n	Mean	(95% CI)	Mean	(95% CI)	
Total-C, *mmol/L*	272	5.7	(5.5, 5.9)	4.9	(4.7, 5.1)	**<0.001**
HDL-C, *mmol/L*	271	1.4	(1.3, 1.4)	1.4	(1.3, 1.4)	0.530
LDL-C, *mmol/L*	272	3.9	(3.8, 4.1)	3.0	(2.9, 3.2)	**<0.001**
TG, *mmol/L*	268	1	(1, 1.1)	1.2	(1.1, 1.2)	**<0.001**
Non-HDL-C, *mmol/L*	270	4.3	(4.1, 4.5)	3.5	(3.3, 3.6)	**<0.001**
ApoA1 *g/L*	251	1.4	(1.3, 1.4)	1.5	(1.4, 1.5)	**<0.001**
ApoB, *g/L*	252	1	(1, 1.1)	1.1	(1.0, 1.1)	0.122
ApoB/ApoA1 ratio	251	0.78	(0.74, 0.82)	0.74	(0.71, 0.78)	0.101
Glucose, *mmol/L*	217	5.1	(5, 5.2)	5.5	(5.3, 5.7)	**<0.001**
HbA1c, %	195	5.4	(5.3, 5.5)	5.7	(5.6, 5.8)	**<0.001**
Systolic BP, *mmHG*	163	129	(126.8, 131.1)	128.6	(127, 130.4)	0.413
Diastolic BP, *mmHG*	163	78.2	(76.8, 79.6)	77.2	(76, 78.5)	0.824

*P <0.05 is considered statistically significant differences between V1 and V3. Tested with paired samples T-test. Significant values in bold. Corrected for multiple testing using False Discovery Rate.

Differences in diet and lifestyle factors

The mean BMI, weight and waist circumference (WC) increased with 1.1 kg/m^2, 2.5 kg and 2,7 cm, respectively, from V1 to V3 (table 14). The proportion of those who were obese increased from 13.3% at V1 to 22.6% at V3. At V1, 54% of those with obesity were female, compared to 44% at V3.

Table 14: Changes in weight, waist circumference and BMI from V1 to V3.

		V3		V1		*p**
TOTAL	n	mean	(95%CI)	mean	(95%CI)	
Weight, kg	243	82.9	(80.8, 85.1)	80.0	(78.1, 82)	**<0.001**
WC, cm	52	99.5	(95.1, 103.8)	95.4	(90.9, 99.9)	**0.002**
BMI, kg/m^2	208	27.3	(26.7, 28)	26.2	(25.5. 26.9)	**<0.001**
MEN						
Weight, kg	128	89.7	(70.3, 75.4)	86.5	(84.1, 88.9)	**0.039**
WC, cm	28	102.8	(96.3, 109.4)	99.7	(92.7, 106.7)	**0.021**
BMI, kg/m2	105	27.7	(26.8, 28.6)	26.7	(25.7, 27.6)	0.082
WOMEN						
Weight, kg	115	75.4	(72.6, 78.2)	72.8	(70.3, 75.4)	**0.001**
WC, cm	24	95.6	(89.9, 101.2)	90.4	(85.2, 95.7)	0.064
BMI, kg/m^2	103	27	(26, 27.9)	25.6	(24.8, 26.7)	**0.002**

*P <0.05 is considered statistically significant differences between V1 and V3, tested with Wilcoxon signed-rank test. Significant values in bold.

The SmD scores improved with 0.9 points from V1 to V3, which is a slight but significant increase from 35.2 points at V1 (p=0.010). At V1, 20.8% of the population were active smokers, while at V3 only 13.6% actively smoked (39% of the population were former smokers at V3), and there were no significant gender differences regarding smoking. The

percentage of those who were physically active ≥ 3 times per week increased from 39.4% to 53% between the visits.

4.2.2 Differences between subgroups

Differences between patients at the lipid clinic and outside of the lipid clinic

The patients outside of the LC were being followed-up at their GP, local hospital or specialist outside of Oslo. When comparing the lipid values between the patients at the LC and those at other institutions, no significant differences were detected (data not shown). There were no significant differences in the prevalence of CVD in each group (30.4% of those at the LC vs 32.7% of those outside). However, significant differences were seen regarding dietary habits in SmD and its subgroups (table 15). The patients who were followed by the LC had significant higher SmD scores than those outside of the LC. The patients at the LC also had significant higher scores regarding healthy dairy choices, but there were no differences in meat, fish and fruits and vegetable intake between the groups.

Table 15: Differences in dietary habits between patients at the LC and outside of the LC.

	Patients at the LC			**Patients outside LC**			***P****
	n	mean	(95%CI)	n	mean	(95%CI)	
SmD score	208	36.2	(35.7, 36.6)	54	34.4	(33.4, 35.4)	**0.026**
Dairy (4-12p)	219	9.9	(9.7, 10.1)	55	8.9	(8.5, 9.3)	**<0.001**
Meat (1-6p)	219	5.6	(5.5, 5.7)	55	5.2	(5, 5.5)	0.104
Fish (1-6p)	219	4	(3.8, 4.1)	55	3.7	(3.4, 4)	0.588
Fruits and vegetables	215	2.1	(2, 2.2)	55	2.2	(2, 2.4)	0.819

*P <0.05 is considered statistically significant differences between patients at the LC and patients outside the LC, tested with Mann-Whitney U-test. Significant values in bold.
SmartDiet; SmD, Lipid clinic; LC.
Max score dairy = 12p, max score meat and fish = 6p, max score fruits and vegetables = 3p.

Differences between patients in high risk and very high risk

According to ESC/EAS guidelines (79), 124 patients were characterized as in VHR, compared to 159 patients when using the NSFA's definition. There were significant differences in some lipid values between those in high risk and VHR (table 16). However, there were no significant differences in the SmD scores, except in the sub groups diary choices and fish intake where the VHR group had a mean score of 9.9 (9.6, 10.2) and 4.1 (3.9, 4.4), respectively. The high-risk group had a mean score of 9.5 (9.2, 9.8) for dairy and 3.8 (3.6, 4.0) for fish intake. The VHR group were older with mean age 61.1 years (59.1, 63.1) compared to those in high risk with mean age 50.4 years (48.5, 52.4). Those in VHR were more intensely medicated, but only 17.4% reached their individual treatment target, compared to 23.7% in the high risk group.

Table 16: Differences in clinical and biochemical measurements between those in high risk and very high risk.

	High risk (ESC/EAS guidelines) n=155			Very high risk (ESC/EAS guidelines) n=124			Very high risk (NSFA's definition) n=159			*P**
	n	mean	(95%CI)	n	mean	(95%CI)	n	mean	(95%CI)	
Total-C, *mmol/L*	152	5.0	(4.8, 5.3)	121	4.7	(4.5, 5.0)	156	4.8	(4.8, 5.3)	0.092
HDL-C, *mmol/L*	152	1.4	(1.4, 1.5)	120	1.3	(1.3, 1.4)	155	1.4	(1.3, 1.4)	**0.019**
LDL-C, *mmol/L*	152	3.2	(3.0, 3.4)	121	2.8	(2.6,3.1)	156	2.9	(2.7, 3.1)	**0.032**
TG, *mmol/L*	152	1.1	(1.0, 1.1)	119	1.3	(1.2, 1.4)	154	1.3	(1.2, 1.4)	**<0.001**
Non-HDL-C, *mmol/L*	151	3.6	(3.4, 3.8)	121	3.3	(3.1, 3.6)	156	3.4	(3.2, 3.6)	0.133
Lp(a) *mg/L*	126	491.5	(377.5, 605.6)	113	645.4	(518.6, 772.1)	143	662.1	(534.1, 790.1)	0.074
ApoA1 *g/L*	146	1.5	(1.4, 1.5)	114	1.5	(1.4, 1.5)	149	1.5	(1.4, 1.5)	0.701
ApoB, *g/L*	147	1.1	(1.0, 1.1)	115	1.1	(1.0, 1.1)	150	1.0	(1.0, 1.1)	0.748
ApoB/ApoA1 ratio	146	0.74	(0.70, 0.79)	114	0.74	(0.69, 0.79)	149	0.73	(0.69, 0.78)	0.948
Glucose, *mmol/L*	131	5.1	(5.0, 5.2)	103	6.1	(5.8, 6.5)	134	6.0	(5.7, 6.2)	**<0.001**
HbA1c, %	128	5.4	(5.3, 5.5)	110	6.0	(5.8, 6.2)	141	5.9	(5.8, 6.1)	**<0.001**
Systolic BP, *mm HG*	117	127	(125, 129)	97	130	(128, 133)	120	130	(128, 133)	0.069
Diastolic BP, *mm HG*	117	77	(76, 79)	97	78	(76, 80)	120	78	(77, 80)	0.347

*P <0.05 is considered statistically significant differences between high risk (ESC) and very high-risk group (ESC) tested with Independent Samples T-Test. Significant values in bold. Corrected for multiple testing using False Discovery Rate.

Differences between those with MetS and those without

At V3, 20.8% of the population was diagnosed with MetS. The group with MetS had a mean age of 61.3 years (58.6, 64), while those not having MetS had a mean age of 54 years (51.8, 55.3). The group with MetS also weights 12.4 kg more ($p<0.001$), with a higher BMI of 4.7 kg/m^2 ($p<0.001$) compared to those who do not have MetS. There were no differences in medication intensity, SmD scores or physical activity between the two groups (data not shown). An overview of the lipid profiles of those with and without MetS are presented in table 17. There were only significant differences between the groups in the blood parameters regarding the MetS criteria (TG, HDL-C, blood pressure and glucose). However, those who had MetS at V3 were not the same people as those in V1. To investigate possible contributing factors in MetS development, four different groups were identified regarding MetS. Those who:

1. Had MetS at V1 but not at V3 (n=11)
2. Developed MetS during the study period (n=39)
3. Had MetS at both V1 and V3 (n=19)
4. Never had MetS (n=210)

Table 17: Differences in clinical and biochemical measurements between those with and without metabolic syndrome.

	With MetS (n=58)			No MetS (n=221)			*P**
	n	mean	(95%CI)	n	mean	(95%CI)	
Total-C, *mmol/L*	58	4.8	(4.4, 5.2)	215	4.9	(4.7, 5.1)	0.549
HDL-C, *mmol/L*	58	1.2	(1.1, 1.3)	214	1.5	(1.4, 1.5)	**<0.001**
LDL-C, *mmol/L*	58	3.0	(2.7, 3.3)	215	3.0	(2.9, 3.2)	0.683
TG, *mmol/L*	57	1.6	(1.5, 1.8)	214	1.0	(1, 1.1)	**<0.001**
Non-HDL-C, *mmol/L*	58	3.6	(3.3, 3.9)	214	3.4	(3.2, 3.6)	0.354
Lp(a), *mg/L*	51	539.8	(361.7, 717.8)	188	570.9	(473.7, 668.1)	0.768
ApoA1 *g/L*	57	1.4	(1.3, 1.5)	203	1.5	(1.5, 1.5)	0.140
ApoB, *g/L*	57	1.1	(1.0, 1.2)	205	1.0	(1.0, 1.1)	0.287
ApoB/ApoA1 ratio	57	0.79	(0.72, 0.85)	203	0.73	(0.69, 0.77)	0.168
Glucose, *mmol/L*	55	6.6	(6.1, 7.2)	179	5.2	(5.1, 5.4)	**<0.001**
HbA1c, %	55	6.2	(5.9, 6.4)	183	5.6	(5.5, 5.6)	**<0.001**
Systolic BP, *mmHG*	50	134	(130, 137)	164	127	(125, 129)	**0.001**
Diastolic BP, *mmHG*	50	78	(76, 81)	163	77	(76, 79)	0.571

*P <0.05 is considered statistically significant differences between those with metabolic syndrome and those without. Tested with Independent Samples T-Test and Mann-Whitney U-test, significant values in bold. Corrected for multiple testing using False Discovery Rate. Values shown in mean (95% CI). Metabolic syndrome; MetS.

When comparing each subgroup of those who 1) had lost, 2) developed, 3) always had or 4) never had MetS during the study period, all groups have shown improvements in SmD scores from V1 to V3 (table 18), but only the group who never had MetS showed significant increase. When comparing the four groups against each other, there were no significant differences in the SmD scores at V3.

Table 18: Comparison of age at V3, weight and SmD scores from V1 to V3 in different metabolic syndrome groups.

	MetS V1, not V3 (n=11)		MetS V3, not V1 (n=39)		MetS V1 and V3 (n=19)		Never MetS (n=210)	
	mean	(95% CI)	mean	(95% CI)	mean	(95% CI)	mean	(95% CI)
Age at V3 (years)	57.1	(50.2, 64.0)	59.8	(56.2, 63.4)	63.0	(58.3, 67.7)	53.5	(51.6, 55.4)
Mean weight at V1	90.1	(75.6, 104.7)	87.0	(80.8, 93.1)	96.4	(76.8, 80.6)	76.4	(74.6, 78.3)
Mean weight at V3	89.3	(72.2, 106.3)	92.5	(86.0, 98.9)	96.2	(87.2, 105.2)	79.4	(77.3, 81.6)
P*	0.800		**0.001**		0.949		**<0.001**	
SmD score at V1	35.1	(31.8, 38.4)	36.0	(34.9, 37.0)	35.5	(33.3, 37.8)	34.8	(34.2, 35.0)
SmD score at V3	35.6	(33.2, 38.1)	36.2	(35.3, 37.1)	37.7	(36.1, 39.4)	35.6	(35.1, 36.1)
P*	0.767		0.349		0.184		**0.040**	

*P <0.05 is considered statistically significant differences in SmD scores between V1 and V3, tested with Wilcoxon Signed Rank Test. Significant values in bold.

Among the 11 people who no longer have MetS at V3, a reduction in TG and an increase in HDL-C were the major contributors in getting rid of the diagnosis. Two of the patients also

managed to get rid of the diagnosis by decreasing their BMI with 7.3 and 5.6 kg/m^2. For the 39 who got the diagnosis at V3, hypertension was the most important contributor, followed by high blood glucose. They also had a significant increase in weight. Among the 19 people who were diagnosed with MetS throughout the study, improvements in TG and HDL-C were detected, while no improvements were found regarding waist circumference, hypertension and blood glucose. Significant weight gain was also observed in the healthy group. Figure 6 shows the change in physical activity in each group.

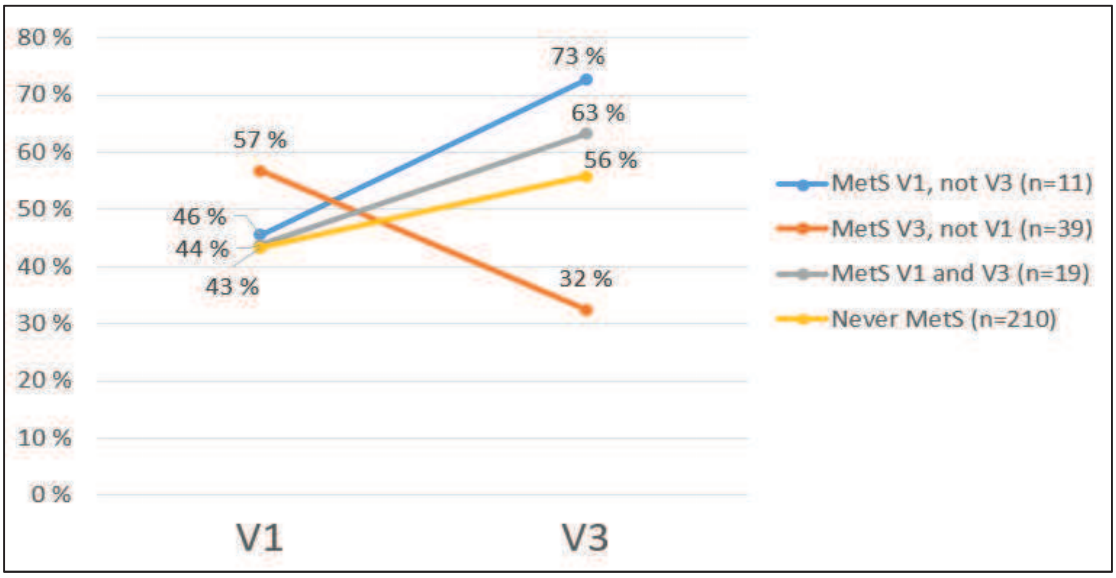

Figure 6: Proportion of those with physical activity more than 3 times/week at V1 and V3. Population divided in different groups of metabolic syndrome.

All groups except those who got MetS at V3, had a higher percentage of physical activity more than three times a week at V3. The group that had MetS throughout the study period had the highest percentage of total CVD, followed by those who developed MetS at V3 (Figure 7).

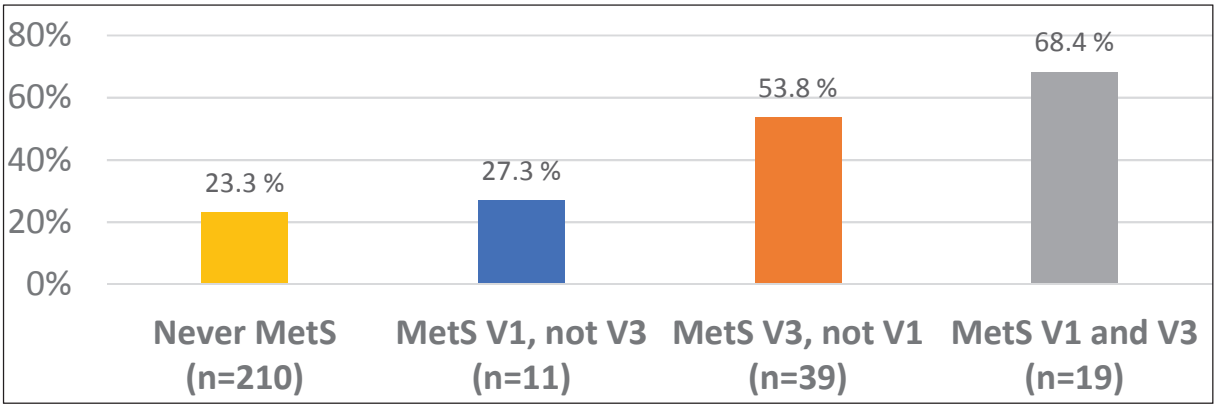

Figure 7: Proportion of those with CVD in different groups of metabolic syndrome. Bars show % of the population in each group. Due to the small number of subjects, regression analysis and trend estimation was not carried out.

Differences between those with CVD and those without CVD

The number of patients who experienced CVD increased from 57 at V1 to 86 at V3, and 63% were male. There were no significant differences in the number of current smokers between the groups. The group with CVD had a significantly higher proportion of former smokers compared to the healthy group (p=0.019). There were no differences in physical activity between the groups. 80.7% of those who experienced CVD before V1 experienced a new CV event between V1 and V3 (Figure 8). The majority of those who had a reoccurrence of CV events were male. To investigate gender differences regarding CVD development, analyses were carried out for men and women separately. The males experienced more CVD at a younger age compared to women, despite similar first measured cholesterol and age of first known elevated cholesterol (table 19).

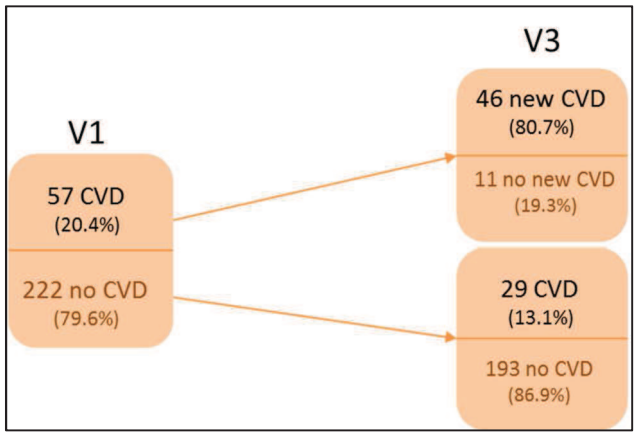

Figure 8: Development of CVD from V1 to V3.

To explore important contributing factors of CVD, the population was separated into three groups, 1) those who have never had CVD, 2) those who had one CV event and 3) those who had multiple CV events. Those with CVD were older and had higher first known cholesterol, age of first measured cholesterol, Lp(a), and more diabetes and hypertension. Those who had experienced CVD were more heavily medicated, concerning both intensity and number of medications compared to the healthy group. 15.1% of those with CVD were treated with PCSK9-inhibitor add-on compared to 5.7% among the healthy patients (data not shown)

Table 19: Comparisons of age at first known elevated cholesterol, age at first CV event and prevalence of CVD between male and female.

	n	Male	n	Female	*P**
Age first known elevated Total-C	149	26.7 (24.4, 29.0)	129	29.3 (26.9, 31.8)	0.117
First measured Total-C, *mmol/L*	143	9.9 (9.5, 10.3)	129	9.7 (9.3, 10.0)	0.335
First measured LDL-C at V0 *mmol/L*	68	7.2 (6.7, 7.8)	67	7.6 (7.1, 8.1)	0.322
Age first CV event	53	45.1 (42.2, 47.9)	30	52.0 (47.8, 56.3)	**0.006**
CVD at all	149	54 (36.2%)	130	32 (24.6%)	**0.038**
Recurrent CVD	149	36 (24.2%)	130	10 (7.7%)	**<0.001**

Data presented as mean (95% CI) or number of patients (% of total in each group).
*P<0.05 indicates significant differences between males and females, tested with students T-test and Fisher's exact test. Significant differences in bold.

Table 20: Comparison of age, biochemical measurements, co-morbidities and medication regimes between those with multiple CV event, one CV event and no CVD.

	No CVD			CVD once			Recurrent CVD			*P**
	N			N			N			
Female	193	98	(50.8%)	40	22	(55%)	46	10	(21.7%)	**0.001**
Current smokers	186	25	(13.4%)	38	4	(10.5%)	45	9	(20.0%)	0.406
Former smokers	166	65	(39.2%)	35	20	(57.1%)	44	24	(54.5%)	0.055
BMI	193	27	(26.3, 27.7)	40	27.3	(25.5, 29.1)	46	27.4	(25.9, 28.9)	0.905
SmD score at V3 [b]	186	34.3	(34.8, 35.8)	37	36.6	(35.5, 37.6)	39	37.4	(36.3, 38.4)	**0.002**
	n	mean	(95%CI)	n	mean	(95%CI)	n	mean	(95%CI)	
Age V3 [abc]	193	51.3	(49.5, 53.1)	40	60.5	(57.1, 63.9)	40	66.7	(64.3, 69.2)	**<0.001**
Age first known elevated total-C [ab]	192	25.2	(23.2, 27.2)	39	32.2	(27.5, 36.9)	39	35.5	(32.6, 38.4)	**<0.001**
Age first CVD [c]			-	38	51.8	(48.3, 55.3)	45	44.0	(40.9, 47.2)	**0.002**
Blood parameters										
First measured Total-C, *mmol/L* [ab]	188	9.3	(9, 9.6)	39	10.5	(9.6, 11.3)	45	11.5	(10.9, 12.1)	**<0.001**
First measured LDL-C, *mmol/L* [b]	102	7.1	(6.7, 7.4)	18	8.2	(6.9, 9.6)	15	8.8	(7.4, 10.2)	0.015
Total-C at V3, *mmol/L*	190	5	(4.8, 5.2)	39	4.5	(4.1, 5)	44	4.7	(4.3, 5.1)	0.147
HDL-C at V3, *mmol/L*	190	1.4	(1.4, 1.5)	39	1.3	(1.2, 1.5)	44	1.3	(1.2, 1.5)	0.383
LDL-C at V3, *mmol/L* [a]	190	3.2	(3, 3.3)	39	2.5	(2.2, 2.9)	44	2.9	(2.5, 3.2)	**0.026**
TG at V3, *mmol/L* [b]	189	1.1	(1.1, 1.2)	39	1.2	(1.1, 1.4)	43	1.3	(1.2, 1.5)	**0.021**
Lp(a) at V3, *mg/L* [b]	161	454.1	(382.0, 526.1)	37	673.7	(385.0, 962.3)	41	898.2	(593.5, 1202.9)	**0.006**
Glucose at V3, *mmol/L* [ab]	163	5.3	(5.1, 5.5)	33	6.1	(5.4, 6.8)	38	6.1	(5.5, 6.7)	**<0.001**
HbA1c at V3, % [ab]	166	5.6	(5.5, 5.7)	33	5.8	(5.6, 6.1)	39	6.1	(5.8, 6.5)	**<0.001**
Co-morbidities at V3	N	n	%	N	n	%	N	n	%	
MetS [ab]	193	24	(12.4%)	40	16	(40%)	46	18	(39.1%)	**<0.001**
Diabetes [b]	193	14	(7.3%)	40	5	(12.5%)	46	9	(19.6%)	**0.043**
Hypertension [abc]	193	22	(11.4%)	40	21	(52.5%)	46	35	(76.1%)	**<0.001**
Lipid lowering medication										
High intensity statin therapy [ab]	193	132	(68.4%)	40	33	(82.5%)	46	41	(83.1%)	**0.006**
Moderate intensity statin therapy [ab]	193	43	(22.3%)	40	5	(12.5%)	46	2	(4.3%)	**0.010**
Single medication	193	39	(20.2%)	40	4	(10%)	46	5	(10.9%	0.143
Double medication [bc]	193	106	(54.9%)	40	21	(52.5%)	46	13	(28.3%)	**0.005**
Triple medication [bc]	193	31	(16.1%)	40	11	(27.5%)	46	23	(50%)	**<0.001**
Quacrouple medication [b]	193	3	(1.6%)	40	2	(5%)	46	4	(8.7%)	**0.024**

*P shows p-value for Kruskal-Wallis test, ANOVA or Fisher's exact test between all three groups, $p<0.05$ is considered significant. Individual Mann-Whitney U-tests were carried out for each group, and multiplied with the number of tests to find differences between specific groups (Bonferroni correction).

[a] Significant differences between «No CVD» and «CVD once» [b] Significant differences between «No CVD» and «Recurrent CVD» [c] Significant differences between «CVD once» and «Recurrent CVD»

5 Discussion

5.1 Discussion of subjects and methods

Study design

The TTT-FH study is a prospective study for assessing the treatment of the HeFH-patients at the Lipid Clinic (LC), Oslo University Hospital (OUS). This thesis is a continuation of three former master's theses conducted during the period of 2015 to 2017. The increased number of participants in this thesis improves the strength of the results, and acts as a quality assessment of the previous findings (115-117).

Visit 2 of the study was conducted shortly after visit 1, while visit 3 was conducted over 8 years later. Only data from V1 and V3 has been used in this thesis to identify long-term changes. Ideally, V3 could have been conducted at only one time point, however the last visit was performed at different time points. Comparisons of the results between all four parts did not give any significant differences, hence these analyses were not included in the result section of this thesis. The results from all four master's theses have been in concordance to each other, which validates the quality of our results.

Participants

When the project started in 2006, all patients at the LC at that time were asked to participate. We expected that some patients either moved out of town or were discharged from the LC during this period of 8-10 years. On the previous master's theses, only patients at the LC participated at V3, however, this thesis included the rest of the study population that was outside of the LC. It was a challenge to find the right contact information of those who were no longer patients at the LC, but we still succeeded to get a participation rate over 60%. Inviting through post, and interviewing most of the participants by phone were also cost efficient.

The study population almost exclusively consists of genetically verified FH-patients, which strengthens the study's results to those with a genetic cause to hypercholesterolemia. In contrast, those with phenotypic FH with a polygenic basis have numerous causes to their high cholesterol (85), which can make it difficult to identify important determinants and customize optimal treatment.

Only 30% of the study population were aware of their high cholesterol earlier than 20 years of age. Since FH is a dominant genetic disease, cascade screening of family members can be an effective tool to reduce the average age at diagnosis, and thereby initiate early treatment to lower the cholesterol burden (118). Several studies have additionally proved that the efficacy and cost effectiveness of cascade screening of children and relatives are favorable (119-121). If we use the age limit for first measured high cholesterol at 20 years or earlier as a proxy for cascade screening, our numbers show that only a small proportion were identified early, and the mean age of first measured cholesterol in our population were almost 30 years. According to all guidelines, treatment of FH should start in childhood. In this respect, the observation that 70% of the patients were aware of their high cholesterol when they were older than 20 years points out a major challenge in the healthcare of FH-patients. It is therefore a goal to increase the frequency and willingness of cascade screening among the patients, especially since the genetic testing in Norway is of high quality with high sensitivity and specificity (122).

Methods

The SmD has been validated for use at the LC to assess the patients' diet according to the heart-friendly recommendations (107). While the form is easy and time-efficient to use, it gives a gross classification of the patient's diet. In clinical use with a dietitian, it is easy to discuss each food group with the patients and recommend dietary changes. However, the SmD makes it difficult to differ between good and bad fat composition in the diet by only looking at the total score. Some food subgroups in the SmD were used in analyses to uncover dietary patterns among FH-patients. However, as with most nutritional research, self-reporting methods are always associated with measurement errors. In our study, an old version of the SmD was used at V3 to make it possible to compare V3 to V1. Since the new and improved versions of SmD were updated according to the popularity of newer products, using the old version might have left out some important dietary factors.

The phone interviews might have given answers that are more reliable on SmD, but were less trustworthy on anthropometric parameters. We expected that the participants in the study were familiar with the SmD since they have been patients at the LC for at least 10 years. Hence, reporting/pleasing bias might have occurred as it is likely that the patients know how to answer in order to get good SmD scores. By interviewing them through the phone, a more reliable answer on SmD might have been achieved because the patients did not fill out the

form physically. The disadvantage with phone interviews instead of normal consultations, is that the patients could not get a traditional doctor assessment with the included clinical aspects. And further, anthropometric measures were either self-reported (weight and height) or skipped (blood pressure and waist circumference).

As with the SmD, the doctor's form is prone to information bias due to the subjective nature of the form. The doctors at the LC address side-effects of drugs by termination and re-initiation of the drug, and investigate whether the side-effects were due to random events. The side-effects can therefore be a result of the doctor's assessment and the patient's conviction to the drug. In order to reduce the impact of information bias, objective variables such as blood parameters were more weighted in the analysis.

The blood parameters in this study were carried out at different laboratories, depending on where the patients chose to go. This makes it difficult to ensure the same quality and analyzing method to all blood results. There were cases where certain analysis could not be done because the blood samples were left out for too long (mainly for glucose, HbA1c and insulin). The results from CRP analysis in this study will not be further discussed. The reasons for this are 1) analyses from different laboratories may give rise to inconsistent results, 2) not all laboratories assess hsCRP, 3) we do not know whether the analytical methods at V1 were the same as V3 and 4) hsCRP assessment should be done continuously within 2 weeks intervals to assess low-grade inflammation.

5.2 Discussion of results

5.2.1 Population characterization and anthropometrics at V3

BMI and obesity

The mean BMI at V3 of our population corresponds to "overweight" and is similar to the BMI of the Norwegian population. With numbers taken from the The Nord-Trøndelag Health Study (HUNT) and The Tromsø Study (Tromsø), the Norwegian Institute of Public Health (NIPH) reports that the majority of the Norwegian population is either overweight or obese (123). Data from HUNT 3 and Tromsø 6 show that the mean BMI were 27.5 kg/m^2 and 26.9 kg/m^2 for men and women in Norway, respectively (124-126). These numbers correspond well to the results in our study population, except the women in our population had a slightly higher BMI at 27.7 kg/m^2. Among men and women between the age of 40-69 in Norway,

25% and 21% were characterized as obese, respectively (3), which is similar to our study population. There is no national data on this topic, and the mentioned studies were conducted only in the regions Trøndelag and Troms in Norway. According to the Statistics Norway (SSB), people in the cities are leaner with a lower prevalence of overweight and obesity than those on the countryside (123, 127).

Other co-morbidities

Type 2 diabetes (T2D) itself is major risk factor of CVD, giving at least a two-fold increased risk (79, 128). Two studies, in Spain and the Netherlands, reported a prevalence of T2D among FH-patients of 1.75% and 5.4%, with an increased prevalence among males, older subjects and higher BMI (129, 130). The prevalence of T2D in our study of 10% was higher than in these two reports. Our findings support the evidence of T2D being more prevalent among males and older people. Comparing to the Norwegian population where 4.6% is diagnosed with diabetes (for those between 40-79 years, the prevalence is 7%), our population has a rather large proportion of diabetes patients (131). However, about half of T2D in the population is undiagnosed (3, 132). Since our FH-patients were followed-up regularly by specialists at the LC, we may expect that most T2D subjects in our study were found and diagnosed. A major drawback to our study is that diabetes treatment was only identified at V3 and not any previous visits, hence we are unable to measure the change in prevalence during 8-12 years of follow-up. Whether the high prevalence of T2D was caused by older age, obesity, statin treatment or other factors cannot be addressed in this study. However, a possible explanation to the high prevalence of diabetes in our population is that statins are somewhat diabetogenic, and the treating physicians at the LC have high diagnostic awareness of diabetes (133).

Similar to the health report in Norway where 25-36% of the population are hypertensive, 28% of our population are receiving antihypertensive drugs (3). When looking at measured blood pressure, under 5 % were qualified as hypertensive. It is encouraging to see that only a small part of the study population has high measured blood pressure at V3, as this is an important contributor to CVD.

Lp(a)

Lp(a) levels were significantly higher among patients with recurrent CV events, and in those who used PCSK9-inhibitors. Also those in VHR and with one CV event had somewhat higher

Lp(a) levels compared to the healthiest group, although the differences were not significant. Both the EAS consensus and American College of Cardiology/American Heart Association (ACC/AHA) guidelines for hypercholesterolemia recommend screening and follow-up for those with Lp(a) levels < 500mg/dL, hence it is important to notice levels above this in our population despite insignificant differences between groups (79, 134). Consistent with the literature, elevated Lp(a) levels were found among those with established CVD, emphasizing an important role of Lp(a) in the development of CVD. To date, there are still no medication that isolated lowers the Lp(a) concentrations substantially, but PCSK9-inhibitors, niacin and apheresis have shown to be useful to lower the concentrations modestly (67). Novel potent Lp(a)-lowering medications are awaited to be developed.

Patients' preferences

The FH-patients acknowledge the importance of diet and lifestyle modification to lower LDL-C, but more people at V3 preferred less side effects over low LDL-C at V3 compared to V1. This suggests that quality of life became more important with increasing age, which was the case among some of the patients. The population generally agrees that a healthy lifestyle plays a major role in risk management, and the majority also wish to achieve the lowest possible cholesterol level. However, the opinions are more spread when it comes to prioritizing low cholesterol levels over their well-being with no side effects. The latter statement was mostly dependent on whether the patient had experienced side effects, and whether these side effects were tolerable or not. Many of those who did not experience any side effects did not "agree" nor "disagree".

5.2.2 Medications and side effects

As recommended by the guidelines, most of the patients were receiving high intensity LLT with statins and ezetimibe. Side effects were most frequent from statin therapy and colesevelam use. The prevalence of side effects from statins in this study was higher than those reported in placebo controlled RCTs. Saxon et. al. proposed that the tendency to find more side effects in clinical practice is because the RCTs do not mirror the diverse patient groups in real life due to the exclusion of certain patients at study start (91). Similar to previous studies on LLT, the most frequent side effects in our population were muscle related symptoms and GI symptoms for statins and colesevelam, respectively. Only 9% of our study population received PCSK9-inhibitors, and none of them reported any noticeable side effectsWhen dividing into definite and probable/possible side effects, under 8% of the users

experienced definite side effects. It is important to bear in mind that this thesis only presents explorative numbers, and studies with larger populations are needed to determine the prevalence of side effects in real life settings and clinical practice.

Patients without statin treatment or any other lipid lowering medication

Our study has a low non-adherence rate to statins compared to the general Norwegian population and FH-patients in the Netherlands. In a register study conducted by the Norwegian Pharmacy Association in Norway, 50% of those with statin prescription stopped using statins after one year (135). The adherence rate was under 40% after two years, and a great proportion did not take out their prescribed medications. In contrast, the adherence rate to statins in our study was over 90%, which indicates better compliance among FH-patients than the general population. A possible explanation could be the high disease awareness and the intensive follow-up by the specialized clinics among our patients.

Those who did not use statins or any LLM were younger than those on statin therapy, and the majority without treatment were female. A study by Galema-Boers et. al. has shown a non-adherence rate to statins of 11% among FH-patients at a lipid clinic in the Netherlands (136). They identified three factors that were associated to non-adherence to statins; 1) younger age, 2) lower untreated TC, and 3) high treated TC. Our results revealed a much lower rate of patients without treatment (8.2% without statins and 6.5% without any LLM). First known cholesterol were also similar among those with and without treatment, and there were no significant age differences in our study. However, the mean age of our study population were 7.5 years older than that of Galema-Boers et.al., which may explain the low non-adherence rate in our study compared to the Dutch subjects.

Our results also revealed a higher non-adherence rate among female FH-patients. Due to natural causes, e.g. pregnancy, females may have more periods without medications. The most common reason for non-adherence in our population was side effects, however it may also be possible that men have received more intense follow-up compared to women. Another note of caution is that general adherence towards treatment regimens was not measure in this study. A new systematic review proposed that the adherence to statin therapy varied from 17.8% to 79.2%, hence there are reasons to believe that these results are prone to underestimations (137).

5.2.3 Changes from visit 1 to visit 3

Dietary habits

According to the SmD, the majority of our FH population have a heart-friendly diet with few areas to improve. The literature on dietary habits among FH-patients, as well as the use of SmD is scarce, and we know little about the real-life adherence to the recommended heart-friendly diet and lifestyle. Dietary management and healthy lifestyle choices are important factors in the treatment of FH. A very small proportion of our study population was classified with an "unhealthy diet" according to the SmD questionnaire. The mean score of our population improved from V1 to V3, and lies on the upper half of the middle category in SmD, reflecting many favorable dietary choices. Still, only 33% of the population is in the best category, meaning there still are potential areas to improve for most of the population. However, a question regarding the relationship between a strict healthy diet and life enjoyment arises. A number of participants stated that even though they always strive to take healthy choices, they still want to "enjoy life" and not be too strict in their dietary patterns. Especially for those who encounter many social settings or live with non-FH people can experience challenges in following strict diets. Could it be that a SmD score in the upper half of the middle category gives the ideal balance between healthy dietary habits and life enjoyment?

Our population showed favorable choices regarding dairy products, meat and fish consumption, but can improve on fruits and vegetable intake. These findings are limited by the gross classification used in the SmD, and can not give us detailed information about the patients' real diet. However, as a tool, SmD enables clinicians to point out specific areas to improve. The scores in our study tells us that low fat dairy and meat products were favored among the patients, as recommended in the guidelines and Norwegian Directorate of Health (80). The score on fish intake also implied a fish consume of at least 2 times per week, which is in line with the Norwegian recommendations for fish intake. The score on fruit and vegetables implied an intake up to 4 units per day, which is lower than the recommended 5 units a day.

It is important to bear in mind that the SmD is especially developed for evaluating a heart friendly diet and is most relevant for patients with dyslipidemias at the LC. This makes it challenging to compare dietary habits with the general population or other patient groups with other measuring tools. It is still encouraging to compare our results to those found by Arroyo-

Olivares et. al. who also reported that FH-patients have healthier dietary habits with greater adherence to the Mediterranean diet compared to their healthy relatives (138). A study conducted on children with FH in Norway also showed that children with FH had healthier food choices, especially regarding saturated fat sources (139). According to the latest nationwide diet survey in Norway, Norkost 3, the Norwegian population still consumes too much saturated fat and too little dietary fiber (140). The consumption of fruits and vegetables ought to be improved in both our study population and in the Norwegian population.

Physical activity

The majority of the FH-patients are physically active for at least 3 times per week. There are limited literature regarding the level of physical activity and adherence to exercise recommendations in the FH-population. According to the national recommendations, adults should be physically active for at least 150 min per week with moderate intensity, or 75 minutes with high intensity. According to Norkost 3, only 20% of the Norwegian population followed this recommendation (140). A drawback of our results is that the amount of physical activity was recorded as session of 30 minutes, with the highest alternative of 3 times per week. This makes it difficult to investigate the real proportion of those who fulfills the national recommendations in our study, and compare it to the general population. Arroyo-Olivares et. al. reported a greater proportion of physical activity among the FH-patients in the SAFEHEART study, however, they found that women were significantly more active than men (138). Our study reported no differences in physical activity between the genders. The possible reporting bias among men, or underreporting in females in our study cannot be ruled out.

Smoking

The number of smokers has been vastly reduced from V1 to V3, and the number of current smokers at V3 were somewhat lower than that in the normal Norwegian population between the age of 45-54 years. Almost 14% of our study population are current smokers at V3. Comparing to the national data, 16% of the Norwegian population between the age of 45 to 54 years are daily smokers by January 2019 (141). There is huge attention on smoking cessation and avoidance of smoke in the treatment of FH-patients. It has been a positive change from V1 where almost 40% of the population was smoking. Though the reduction in the number of smokers is substantial, the current smokers at V3 still have a seriously elevated risk of CVD. As there are limited studies reporting the actual prevalence of smokers among

FH-patients in Norway, these preliminary results highlight an important issue for further research and enhanced treatment focus.

Obesity

The prevalence of obesity in the study population increased from V1 to V3. Also in the HUNT study and the Tromsø study, the prevalence of obesity increased during the 8-12 years of follow-up. Data from HUNT 2 and HUNT 3 showed that the prevalence of obesity increased with 7.7% and 4.8% for men and women, respectively, through 11 years (142). Likewise, Tromsø 4-6, which spans over 13 years, showed an increase in the prevalence of obesity with 11% and 9.1% for men and women, respectively (125). In our study, the increase of obesity is also most prominent among males. Though it is important to notice that due to the small sample size, conclusive statements could not be drawn regarding obesity development in our population. However, since increasing BMI is associated with higher risk of cardiovascular morbidity and mortality, this weight gain on top of the cholesterol-burden is very unfortunate for our patients (143, 144).

Blood parameters and achievement of treatment targets

The number of patients reaching their individual treatment targets increased with 16% from V1 to V3. Despite the use of high intensity LLT, the population is still far from reaching the mildest treatment target of LDL-C < 2.5 mmol/L. Similar findings have been documented in other previous studies, although not in Norway (145-147). In those studies, the percentage of those who reached the target of LDL-C < 2.5 mmol/L with traditional maximal LLT were on average between 11.2-26.9%, with the Netherlands having one of the highest percentage (147). Our finding of 26.5% reaching LDL-C < 2.5 mmol/L implies similar responses to maximal LLT in Norwegian FH-patients. However, it is important to highlight that a reduction in LDL-C has a cumulative effect over time by reducing the overall LDL-C burden. In addition to aiming at an absolute treatment goal, adherence to treatment and long-lasting reduction in cholesterol is also important.

A higher proportion of those with high intensity LLT succeeded in reaching their treatment goal of LDL-C < 2.5 mmol/L compared to those on moderate intensity LLT. However, no more than 8-9% in both the group with high intensity and moderate intensity LLT were able to reach the goal of LDL < 1.8 mmol/L. This indicates that traditional maximal LLT alone may not be sufficient in reaching target LDL-C. Adding novel treatment options, like PCSK9-

inhibitors, are shown to be promising and may potentially result in more patients reaching their treatment targets (145-147). Our data so far indicate that even using PCSK9-inhibitors, no more than half of these patients were able to reach their treatment targets. A limitation to these results are the low number of participants and patients receiving PCSK9-inhibitors in this study.

5.2.4 Differences between subgroups

Differences between patients at the LC and outside the LC

The patients treated outside of the LC had similar lipid profiles as the patients at the LC, but they had lower dietary scores. Those who have not had any follow-up at the LC during the last three years, and those who were no longer patients at the LC were included in our study population. They were discharged from the LC because they were either optimally treated and had stable lipid values (most common), or they had moved outside of Oslo. There were no differences in CVD prevalence between patients at the LC and patients outside of the LC. There were no differences regarding lifestyle or anthropometric measurements between the two groups. In reviewing the literature, data on the differences between FH-patients in lipid centers or LCs vs discharged patients are scarce. In principle, the patients who are no longer followed at the LC have access to the same prescribed treatments at their GP, other hospitals and institutions. The main differences between the two patient groups were the availability of a dietitian with dietary advices, and the repeatable filling of SmD at each visit, which the different dietary scores may reflect.

Patients in high risk and very high risk

Over half of the study population are in VHR group of developing CVD. The FH diagnosis itself is a major risk factor for CVD, which leaves the whole study population in the high-risk group initially. However, since the CVD risk increases exponentially with every additional number of risk factors, the cardiovascular risk factors have synergistic effects on total risk, rather than additive (148). According to Wilson et. al., a cluster of three or more risk factors can result in 2.39-5.90 times higher risk of CHD (149). When taken these factors into account, almost 3/5 of the population has additional risk factors putting them into the VHR group.

The current guidelines from ESC/EAS for identifying patients in VHR underestimates the prevalence of VHR patients compared to the NSFA's definition. The differences between

ESC/EAS and NFSA is the inclusion of untreated patients before 40 years in the French definition. When using the ESC/EAS guidelines, 13% of our population were left out of the VHR group. A study from France, similar to this master's project, used the definition by the NSFA. They reported that VHR patients had more advanced carotid plaques and were heavier medicated compared to those in high-risk, even though the LDL-C values between the groups did not differ (150). Pérez-Garcia et. al. have also shown that the odd ratio of CHD is 6.40 for those who started treatment older than 40 years (111). This underlines the great importance of early detection and intensive treatment to reduce the risk of CVD for people with late diagnosis and treatment start. When using the ESC/EAS guidelines, we may potentially leave out patients who really are in the VHR-group.

Metabolic syndrome

No apparent differences in lipids or dietary habits were detected between those with MetS and those without MetS at V3. The prevalence of MetS increased from V1 to V3, which is concerning. Significant differences in clinical and biochemical measurements were detected for the parameters involved in the definition of MetS (hypertension, diabetes, TG, HDL-C and BMI). This study has been unable to demonstrate any differences in dietary habits through SmD between those with MetS at V3 and those without. A reason for this might be that the SmD only evaluates food groups according to fat and sugar quality, without assessing the total energy consumed. High energy intake and low energy expenditure are common reasons for weight gain in adults (151). We therefore believe that an imbalance between energy intake and energy expenditure was not detected due to the form of SmD. An overestimation of physical activity and/or incorrect report of dietary intake could also have occurred.

The patients who developed MetS during the study were less physically active at V3 compared to V1. To investigate important factors in the development of MetS, the population were separated into four groups based on when they had MetS. Physical activity is associated with a wide range of health benefits, including protection against MetS and chronic diseases (80). When looking at the physical activity level of the group who developed MetS at V3, our study supports evidence from previous observations that physical inactivity is associated with increased prevalence of MetS (152, 153). In addition, the group who initially had MetS at V1 and then got rid of the diagnosis at V3 became the most active group at V3. A significant weight gain was observed among those who acquired MetS at V3, which further indicates an imbalance between energy intake and expenditure in this group. Taken together, results from

the present study underlines the importance of encouraging FH-patients to be physically active.

The prevalence of CVD were highest among those who have had MetS the longest time (group 3), compared to those who did not have MetS (group 4). In accordance with previous studies, the presence of MetS increases the risk and prevalence of CVD (154). Our results also highlight the role of the severity of MetS where 68.4% of those who have always had MetS (group 3) experienced CVD. The prevalence of CVD decreased to 53.8%, 27.3% and 23.3% among those who developed (group 2), had lost (group 1) and never had MetS (group 4), respectively. A possible explanation can be the major negative impact of metabolic abnormalities in MetS on CVD mortality, as mentioned in a meta-analysis by Fan. et al. (155). The group who got rid of their MetS diagnosis (group 1) had a prevalence of CVD that were similar to the group who never had MetS (group 4), which underlines the positive effect of treating MetS. However, the sample size in our study are too small to make any conclusive statements. This rises important issues for further research and treatment development of MetS among FH-patients.

Cardiovascular disease

Those with CVD had heavier risk profiles compared to the healthy group, even though the CVD groups had lower LDL-C at V3. What stands out is that those who had experienced CV events became aware of their high cholesterol at an average age of 34 years, which is 8.8 years later than the healthy group. Further, the first measured TC level among those with CVD were 11 mmol/L compared to 9.3 mmol/L in the healthy group. This emphasizes the problem of underdiagnosing and undertreating FH-patients (85). Another important finding is higher Lp(a) levels in those with multiple CV events. Those with CVD had lower LDL-C at V3, probably due to the high intensity treatment. The mean age of the healthy group at V3 is similar to the mean age of the first CV event of the groups with CVD. This can indicate successful prevention at an earlier age resulting in postponement of disease development in the healthy group.

Our results indicate that high first known cholesterol value, high age of first measured cholesterol level, high Lp(a) concentration, diabetes, hypertension and older age contribute to higher CVD risk. However, we could not analyze how strongly each factor contributed to the elevated CVD risk. Those with CVD had more MetS, diabetes and hypertension compared to

those without CVD. Those with recurrent CVD had even more hypertension than those with only one CV event. The differences in the number of current smokers at V3 between those who had CVD and the healthy group was not significant. However, a larger proportion of those with CVD were former smokers compared to the healthy group (55.8% vs. 39.2%, p=0.016), which emphasizes smoking as a serious risk factor of CVD. Our analysis showed that those with CVD had better SmD scores than those without CVD. Better dietary habits and lipid profiles among those with CVD may indicate intensified follow-up by the treating physicians, but can also imply higher awareness of risk factors among the patients.

Gender differences in blood parameters and CVD

Interestingly, the women had higher LDL-C values and also less intensive LLT, but less CVD than men at V3. Statin treatment reduced the untreated TC levels in the population with 50%. When looking at the genders individually, the men reduced their untreated levels with 54.5% while the women only reduced with 45.4%. In our material, a larger proportion of those with no treatment were female. However, when excluding those without LLT, we still observed the same differences between men and women. These findings are similar to those of Doi et. al, who argued that there are less atherogenic risk among women despite less treatment and less favorable the LDL-C values (156). When looking at the SmD scores and smoking status, there were no significant differences between the genders.

The women had their first CV event later than the men, and a higher percentage of those with recurrent CVD were men in our population. Similar to Mundal et. al., the age of first CV event among men were 45.1 years (38). In contrast, the women in our population had their first CV event 6.9 years later than the men. In the article by Mundal et. al., the women were diagnosed significantly later than the men. In our population, the patients were aware of their hypercholesterolemia before 30 years, and there were no age differences between the genders. This may imply that early awareness and initiation of statin treatment can postpone CV events in women. Men typically have more severe atherosclerosis and develop CAD earlier than women, implying that the development of atherosclerosis may impact men and women somewhat differently (157-159). However, the reason why women are more protected against atherosclerosis prior to menopause is still poorly understood.

6 Conclusion and future perspectives

Our study showed that:

- The study population had a mean BMI corresponding to “overweight”. Their mean BMI were similar to the Norwegian population. 10% of the population had diabetes and 28% were treated for hypertension.

- The mean BMI, weight and WC in the population increased from V1 to V3, and the prevalence of obesity increased from 13.3% to 22.6%. The prevalence of MetS increased from 10.8% at V1 to 20.8% at V3.

- The majority of our population received high intensity LLT, with the statin-ezetimibe combination being the most common. Only 9% of the population were using PCSK9-inhibitors. The FH-patients very high adherence rate to their LLM. 34% experienced side effects, mostly muscular symptoms from statins and abdominal discomfort from colesevelam.

- There were significant reductions in mean TC, LDL-C, and non-HDL-C between V1 and V3. Mean plasma glucose, HbA1c, and TG significantly increased during the study period. The population had a heart-friendly diet that persisted for median 10 years. Most (74%) of all identified smokers at V1 had quit smoking by the time at V3. Over half of the population were physically active at least 3 times a week.

- CVD were present in 20.4 % at V1 and 30.8% of the population at V3. 80 % of those who experienced CV events at V1 experienced at least one new CV event during the 8-12 years follow-up. The majority of those with recurrent CVD were males.

When comparing the different subgroups, we found that

- There were no differences in lipid values between patients at the LC and patients treated outside the LC. The only significant difference between the groups were their SmD scores. The patients at the clinic had higher dietary scores compared to those outside the clinic.

- There were no differences in lipid values or SmD scores between those in high risk and those in VHR. When comparing definitions for patients in VHR from ESC/EAS guidelines and NSFA's guidelines, ESC/EAS underestimates the number of patients in VHR. Thirty-five patients were excluded from the VHR group when using ESC/EAS guidelines due to the exclusion of those untreated before 40 years in their definition.

- There were no differences in blood parameters between those with and those without MetS at V3, except for the values included in the definition for MetS (HDL-C, TG, glucose and systolic blood pressure). Those who acquired MetS during the study period were less physically active at V3 compared to V1.

- Those with CVD had a higher prevalence of hypertension, diabetes, MetS and higher first measured cholesterol compared to the healthy group. Those with CVD were also aware of their hypercholesterolemia 8.8 years later than the healthy group.

- There were no differences in the time or level of first known elevated cholesterol level between males and females. At V3, the females had higher LDL-C compared to males, and they were less intensely medicated. The females experienced less CVD and at an older age compared to males.

This study have discovered trends showing increases of MetS and weight gain in spite of close follow-up from the clinics. Further, we also found tendencies of more CVD among those who have had MetS in a longer period of time. Futures studies with larger samples on the prognosis and adherence to treatment in the FH population are recommended to improve treatment and prevention of all risk factors, not only LDL-C. Despite the small sample size and insecurities in this study, several important issues were raised regarding the actual treatment of this patient group. Early identification and treatment, prevention of MetS and hypertension, as well as maintaining a healthy lifestyle with physical activity seem to be important factors in preventing CVD alongside LDL-C reduction. Further studies in the FH-population regarding different co-morbidities and lifestyle changes would be of great use for better healthcare and treatment development.

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Appendices

Appendix 1 The doctor's form

Appendix 2 SmartDiet version 2003

Appendix 3 The patient's preference form

Appendix 4 Approvals by the Regional Ethical Committee for Medical Research

SCREENINGSNR:_____ INITIALER:_____ DATO:_____

TTTFH VISITT 3

Medikasjon

Medikament (navn)	Grunn, indikasjon	Startet dato dag/mnd/år	Sluttet dato Dag/mnd/år	Brukes fortsatt JA
				☐
				☐
				☐
				☐
				☐
				☐

Bivirkninger ved dagens lipidmidler

1 = sikkert, 2 = sannsynlig, 3 = mulig, 4 = nei

	Nåværende medisiner			Tidligere medisiner		
Dagens medikament	_____	_____	_____	_____	_____	_____
Bivirkning 1-4	_____	_____	_____	_____	_____	_____
Type, beskriv	_____	_____	_____	_____	_____	_____

Kun lege:

Øker du lipidmedisineringen for å oppnå behandlingsmål? ☐ **Nei** ☐ **Ja**

Grunnene til å ikke øke lipidmedikasjon:

- ☐ Pasient vil ikke/ er skeptisk etc…
- ☐ Behandlingsmålet er nådd
- ☐ Pga bivirkninger
- ☐ Legen ser det an (kostsvikt, annen variasjon), nye 6 prøveuker
- ☐ Legen vil ikke ut fra samlet vurdering (mulig bivirkning, interaksjonsfare, polyfarmasi, ikke alvorlig familierisiko, pasientens holdning, etc)
- ☐ Har maks tålbar medikasjon/maks av det som var før PCSK9-hemmer
- ☐ Graviditetsønske
- ☐ Annet, beskriv _____

Hvordan endres lipidmedikasjon:

- ☐ Øker dosen av samme statin statin_____ fra dose_____ til dose_____
- ☐ Reduserer dose samme statin statin_____ fra dose_____ til dose_____
- ☐ Bytter til sterkere statin fra statin_____ fra dose_____ til dose_____
- ☐ Bytter til svakere statin fra statin_____ fra dose_____ til dose_____
- ☐ Legger til ☐ ezetimibe ☐ colesevelam ☐PCSK9-hemmer ☐ Niaspan
- ☐ Legger til Inegy dose_____

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SCREENINGSNR:_____ INITIALER:_____ DATO:_____

Hvis pasienten har sluttet på lipidmedikasjon

Avsluttet medikament	**Grunnen til det**	**Avsluttet når Dag/mnd/år**	**Fortsatt uten**
			☐
			☐
			☐
			☐

Hvis pasienten har hatt lange *pause* i lipidmedikasjon

Medikament	**Grunn til pause** **Barneønske/gravid/amming** **Prosjekter** **Reise** **Non compliant** **Annen sykdom**	**Pause start Dag/mnd/år**	**Pause stopp Dag/mnd/år**	**Fortsatt uten**
				☐
				☐
				☐
				☐

Viktige tidsforløp

Når kom pasienten til Lipidklinikken? _____

	Resin hos barn	Statin	Dobbelmedikasjon Type	Trippelmedikasjon type
Når startet lipidmedikasjon?	_____	_____	☐	☐
			☐	☐
				☐

Når sluttet oppfølgingen _____

- ☐ Ønsket selv ikke oppfølging
- ☐ Ikke møtt ved flere innkallinger
- ☐ Avviklet av oss og følges opp ved fastlege
- ☐ Avviklet av oss og følges ved sykehus/annen lipidklinikk
- ☐ Ønsket selv ikke, pga annen sykdom
- ☐ Død. Årsak_____

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SCREENINGSNR:_____ INITIALER:_____ DATO:_____

ADVERSE EVENTS

☐ **Ingen medisinske hendelser siden frem til i dag (hopp over neste skjema)**

Adverse event (diagnose)				
Startdato	(dd/mm/åå)	(dd/mm/åå)	(dd/mm/åå)	(dd/mm/åå)
Alvorlighet	☐ 1 mild ☐ 2 moderat ☐ 3 alvorlig	☐ 1 mild ☐ 2 moderat ☐ 3 alvorlig	☐ 1 mild ☐ 2 moderat ☐ 3 alvorlig	☐ 1 mild ☐ 2 moderat ☐ 3 alvorlig
Tiltak Lipidmedisiner ble	☐ 1 øket ☐ 2 redusert ☐ 3 stoppet midlertidig ☐ 4 stoppet permanent	☐ 1 øket ☐ 2 redusert ☐ 3 stoppet midlertidig ☐ 4 stoppet permanent	☐ 1 øket ☐ 2 redusert ☐ 3 stoppet midlertidig ☐ 4 stoppet permanent	☐ 1 øket ☐ 2 redusert ☐ 3 stoppet midlertidig ☐ 4 stoppet permanent
Hvilken lipidmedisin	_____	_____	_____	_____
Annen medik ble gitt	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei
Annet/opr etc	_____ _____	_____ _____	_____ _____	_____ _____
Ingen tiltak	☐	☐	☐	☐
Do serious criteria apply?	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei
Outcome, still present? Dato løst	☐ Ja ☐ ukjent ☐ Nei - løst	☐ Ja ☐ ukjent ☐ Nei - løst	☐ Ja ☐ ukjent ☐ Nei - løst	☐ Ja ☐ ukjent ☐ Nei - løst
Årsak Adverse event skyldes lipidmidler	☐ 1 Ja, sannsynlig ☐ 2 Ja, mulig ☐ 3 Nei, usannsynlig ☐ 4 Nei, sikkert	☐ 1 Ja, sannsynlig ☐ 2 Ja, mulig ☐ 3 Nei, usannsynlig ☐ 4 Nei, sikkert	☐ 1 Ja, sannsynlig ☐ 2 Ja, mulig ☐ 3 Nei, usannsynlig ☐ 4 Nei, sikkert	☐ 1 Ja, sannsynlig ☐ 2 Ja, mulig ☐ 3 Nei, usannsynlig ☐ 4 Nei, sikkert
Hvis nei, var årsaken? Kardiovaskulær sykdom Type:	☐ Ja	☐ Ja	☐ Ja	☐ Ja
Annen sykdom Type:	☐ Ja	☐ Ja	☐ Ja	☐ Ja
Annen medikasjon (concommitant) Type:	☐ Ja	☐ Ja	☐ Ja	☐ Ja
Annet Beskriv:	☐ Ja	☐ Ja	☐ Ja	☐ Ja

Har det vært potensielt endepunkt frem til i dag? ☐ Ja ☐ Nei **(**Hvis ja, se eget skjema)

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SCREENINGSNR:_____ INITIALER:_____ DATO:_____

Pasientens status i dag

SOSIALT

☐ Skoleelev/student/lærling ☐ Fulltidsjobb ☐ Deltidsjobb
☐ Hjemmeværende ☐ Sykemeldt ☐ Attføring/rehabilitering etc
☐ Arbeidsledig ☐ Delvis uførepensjon ☐ Full uførepensjon

☐ Bor alene ☐ Samboer/gift ☐ Bor med foreldre/søsken/slekt

KOST

Har du gjort store endringer i kosten det siste året? ☐ Ja ☐ Nei
Beskriv:

Poeng SmartDiet:_____

RØYKING

Endringer den siste tiden? ☐ Ja ☐ Nei Beskriv:

☐ Aldri røkt ☐ Tidligere røkt Startet første gang: _____ Sluttet siste gang: _____

☐ Sigaretter Antall per dag: _____

☐ Pipe/cigarillos Antall per dag: _____

ALKOHOL

Endringer den siste tiden? ☐ Ja ☐ Nei Beskriv:

Antall enheter per uke: _____

TRNEING

Endringer den siste tiden? ☐ Ja ☐ Nei Beskriv:

Type_____ Tid per uke _____
Type_____ Tid per uke _____
Type_____ Tid per uke _____
Type_____ Tid per uke _____
Type_____ Tid per uke _____

FEMALE OF CHILDBEARING POTENTIAL ☐ Ja ☐ Nei

Hvis JA, prevensjon: ☐ P-piller ☐ Annet_____ ☐ Intet

Hvis NEI, hvorfor: ☐ ≥ 2 år siden menopause ☐ Annet_____ ☐ Sterilisert

MEDIKAMENT ALLERGI

Medikament: _____ Type reaksjon: _____
_____ _____
_____ _____
_____ _____

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TTT-FH 2018

SCREENINGSNR:_____ INITIALER:_____ DATO:_____

Hvis det er potensielt endepunkt, fyll ut (1 skjema per endepunkt):

<table>
<tr><th colspan="2">POTENSIELLE ENDEPUNKTER</th></tr>
<tr><td colspan="2">KUN 1 KRYSS</td></tr>
<tr><td>☐ Suspected or confirmed non fatal acute MI</td><td>☐ Hospitalization with primary diagnosis of CHF</td></tr>
<tr><td>☐ Death – coronary</td><td rowspan="2">☐ Cerebrovascular Event
• Fatal stroke
• Non-fatal stroke
• TIA</td></tr>
<tr><td>☐ Death – other</td></tr>
<tr><td rowspan="2">☐ Coronary revascularication Procedure
• Coronary artery bypass graft (CABG)
• PTCA (includes atherectomy and stent implantation)
• Other coronary revascularization procedure</td><td>☐ First diagnosis of PVD</td></tr>
<tr><td>☐ Hospitalized PVD event</td></tr>
<tr><td>☐ Documented angina</td><td>☐ Other non-CHD vascular events</td></tr>
</table>

Date of event: _____

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: _____ Discharge date:_____

AV Phung, KE Arnesen, K Retterstøl
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Appendix 2

SmartDiet

20 spørsmål om ditt kosthold og din livsstil

Navn: .....

Fødselsdato: .....

Dato for besvarelsen: .....

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

Les spørsmålene og de angitte svarmulighetene nøye!
Angi gjerne hva du spiser med en strek under matvaren(e).

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

1. Melk (sur/søt)

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

Hvilken type bruker du oftest? *Som drikk, på gryn, grøt, dessert, i kaffe/te.*

Helmelk • Kulturmelk • Kefir • Kaffemelk 5% fett .....

Lettmelk • Cultura • Biola (syrnet lettmelk) • Ekstra Lett melk .....

Skummet melk • Skummet kultur melk • Biola bærdrikk (0,1% fett) .....

Drikker / bruker melk sjelden eller aldri .....

2. Fløte, rømme og lignende

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

Kremfløte • Pisket krem • Crème Fraiche • Seterrømme .....

Kaffefløte • Matfløte • Vikingmelk • Kesam (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 • loff • fine rundstykker • lyst knekkebrød • baguetter • riskaker • puffet ris • cornflakes • havrenøtter • 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.....

4. Smør, margarin på brødmaten

Hvilken type bruker du oftest?

Meierismør • Tine smør (mykere) • Tine setersmør • Smøregod • Bremyk • Brelett • Melange margarin • Per margarin • Soft flora stekemargarin (kube) • Soya stekemargarin (kube) • Soft margarin uten salt og melk • Letta .....

Soft Flora (beger) • Soft Light • Soya margarin (beger) • Soya lett margarin • Oliven margarin • Olivero • Solsikke margarin .....

Vita • Vita lett • Omega .....

Bruker vanligvis ikke smør eller margarin på brødmaten .....

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

Hvor mange skiver brød / knekkebrød med ost spiser du daglig? Antall:____

Hvilken type bruker du oftest?

Hvitost (F45) • Nøkkelost (F45) • Gudbrandsdalsost (G35) • Ekte geitost • Fløtemysost • Edamer • Gräddost • "Dessert oster" • Smørbare fete oster (H50 og fetere) • Mozzarella (mer enn 20% fett) • Feta ost (mer enn 20% fett) • Revet pizza-/pastaost • Taffelost • Burgerost • Snøfrisk, smørbar geitost • Parmesan .....

Lettere hvitost • Lettere nøkkelost • Lettere fløtemysost • Lettere Gudbrandsdalsost • Smørbare oster (16% fett) • Mozzarella (16% fett) • Fetaost (20% fett) • Prim med vaniljesmak.....

Cottage cheese • Gamalost • Pultost • Mager mysost • Prim • Mager prim • Smørbar magerost .....

Bruker ost to ganger eller sjeldnere i uken, eller bruker aldri ost .....

6. Kjøttpålegg

Hvilken type bruker du oftest?

Leverpostei • Salami • Lett salami/spesialsalami • Servelat • Fårepølse • Falukorv Fleskepølse • Morrpølse • Reinsdyrpølse • Stabburpølse • Sylte • Lammerull.....

Lett/mager leverpostei • Lett servelat • Delikat ovnsbakt postei .....

Bankekjøtt • Kalkunpålegg • Kyllingpålegg • 3% servelat (Det Sunne Kjøkken) • 3% leverpostei (Det Sunne Kjøkken) • Kalverull • Okserull • Skinke kokt/røkt • Hamburgerrygg • Annet kjøtt uten synlig fett .....

Bruker ikke kjøttpålegg ukentlig eller bruker aldri kjøttpålegg .....

7. Fiskepålegg

Hvor ofte har du fiskepålegg på brødmaten?

Laks • makrell • sild • sardiner • brisling • tunfisk • reker • krabbe • crab-sticks • fiskepudding • fiskekaker • Havbris etc.

På inntil 1 brødskive i uken, eller aldri .....

På 2 til 4 brødskiver i uken .....

På 5 eller flere brødskiver i uken .....

8. Majones, majonespålegg

Hvor ofte har du majonespålegg på brødmaten?

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

På inntil 1 brødskive i uken, eller aldri .....

På 2 til 7 brødskiver i uken .....

På 8 eller flere brødskiver i uken .....

9. Kjøtt til middag

Hvilken type bruker du oftest?

Også medregnet kjøtt i sammensatte retter som pizza, lasagne, pastaretter, gryteretter, lapskaus, taco og lignende og bacon til frokost

Grillpølse • Wienerpølse • Kjøttpølse • Knakkpølse • Nakkekoteletter med fettrand • Lammekoteletter • Medisterfarse • Medisterpølse • Medisterdeig • Medisterkake • Wienerschnitzel • Fenalår • Bacon med fettrand • Flesk • Grillben • Fårekjøtt • Pinnekjøtt • Ribbe • And • Gås .....

Kjøttdeig • Kjøttkaker • Kjøttpudding • Kjøpte karbonader • Hamburger • Kebabkjøtt • Leverpølse • 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, Kjøttpudding og Karbonader med 3% fett ("Det Sunne Kjøkken") • Grill- og kjøttpølser med 9% fett ("Go' og Mager" fra Gilde) • Viltkjøtt • Kalv • Lam indrefilet • 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 (kube) • Per margarin (kube) • Soft Flora stekemargarin (kube) • Soya stekemargarin (kube) .....

Soft Flora (beger) • Soya margarin, (beger) • Solsikke margarin • Oliven margarin • Olivero .....

Olje • Flytende margarin • Vita • Omega .....

Bruker vanligvis ikke fett i matlagingen .....

12. Grønnsaker

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

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

0 til 1 daglig .....

2 daglig .....

3 eller flere .....

13. Frukt, bær, juice

Hvor mange porsjoner spiser/drikker du daglig?

1 porsjon = 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 søt drikke

Hvor ofte spiser/drikker du dette?

1 brødskive med honning, syltetøy, prim, brunost, sjokoladepålegg eller annet søtt pålegg; 1 glass sukret 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 • mager bakst (som gjærbakst) • saftis, 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 sigaretter/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 brennevin (drink, konjakk, 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:

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

DATO:_____

SCREENINGSNR:_____ INITIALER:_____

Intensiv pasientoppfølging – hvor fornøyd er du med det?

Kjære pasient!

Ved Lipidklinikken ønsker vi en tett oppfølging for å senke kolesterol 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.

1. Hvor får du hovedoppfølgingen av din FH?

- ☐ Fastlegen
- ☐ Sykehus
- ☐ Lipidklinikken
- ☐ Ingen

2. Hvor ofte er du hos fastlegen/andre behandlingssteder?

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

SNU ARKET!

AV Phung, KE Arnesen, K Retterstøl
TTT-FH 2018

DATO:_____

Hva synes du følgende utsagn:

5. 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

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

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

7. 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

8. Jeg ønsker at kolesterolverdien blir så lav som mulig

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

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

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

Andre kommentarer:

_____

AV Phung, KE Arnesen, K Retterstøl
TTT-FH 2018

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

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

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
Prosjektleder: 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 prognosen 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.

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

Komiteens vurdering

Av søknadsskjemaet 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 forståes 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 søknad 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 avidentifisert, 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 Helsedirektoratets 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 søknaden, 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

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Elin Evju Sagbakken	22845502	08.08.2018	2014/753/REK sør-øst A
			Deres dato:	Deres referanse:
			25.07.2018	

Vår referanse må oppgis ved alle henvendelser

Kjell-Erik Arnesen
Medisinsk klinikk

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

Forskningsansvarlig: Oslo universitetssykehus HF
Prosjektleder: Kjell-Erik Arnesen

Vi viser til søknad om prosjektendring datert 25.07.2018 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering

REK har vurdert følgende endringer i prosjektet.

1. Ny kontaktperson ved forskningsansvarlig institusjon, Lene Kristine Seland, Avdelingsleder, OUS

2. Ny prosjektmedarbeider, Masterstudent, Ann Vinh Phung.

3.Utvidelse av prosjektperioden med halvannet år, til 31.07.2019.

4.110 pasienter inviteres til ny konsultasjon ved Lipidklinikken, ved fremmøte eller telefonintervju. De skjema vi tidligere har redegjort for ved forrige mastergrad i 2017, brukes også under intervjuet

Komiteens leder har vurdert søknaden og har ingen innvendinger til de søkte endringer.

Vedtak

Komiteen godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres ytterligere endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende ny endringsmelding til REK.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal deretter slettes eller anonymiseres.

Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder

for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding til REK, se helseforskningsloven § 12, senest 6 måneder etter at prosjektet er avsluttet.

Klageadgang

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.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår portal:

https://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på epost til: post@helseforskning.etikk.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Elin Evju Sagbakken
Seniorrådgiver og Komitésekretær

Kopi til: *oushfdlgodkjenning@ous-hf.no*