Treat-To-Target Familial Hypercholesterolemia

A prospective study of effects from aggressive lipid lowering treatment in an outpatient setting during eight to ten years in patients with Familial Hypercholesterolemia

Master thesis by Irene Mork

Department of Nutrition, Faculty of Medicine
University of Oslo

November 2016

Treat-To-Target Familial Hypercholesterolemia

A prospective study of effects from aggressive lipid lowering treatment in an outpatient setting during eight to ten years in patients with Familial Hypercholesterolemia.

Master thesis by Irene Mork

Supervisors: Kjell-Erik Arnesen and Kjetil Retterstøl

Department of Nutrition, Faculty of Medicine
University of Oslo

November 2016

2016

Treat-To-Target Familial Hypercholesterolemia

- *A prospective study of effects from aggressive lipid lowering treatment in an outpatient setting during eight to ten years in patients with Familial Hypercholesterolemia*

http://www.duo.uio.no/

Trykk: CopyCat, Nydalen.

Summary

Introduction and aims: Familial hypercholesterolemia (FH) is an autosomal dominant genetic disease, characterized by severely elevated LDL-cholesterol (LDL-C), accelerated atherosclerosis and premature cardiovascular disease (CVD). Early detection and initiation of lipid lowering treatment (LLT) is crucial to reduce the risk of premature CVD. Moreover, all modifiable CVD risk factors should be optimally treated to prevent further excess risk. The aim of this thesis is to describe the effects of aggressive LLT in an outpatient lipid clinic over an eight to ten years period. Specifically, we focus on lipid levels and other blood parameters, anthropometry, diet and lifestyle, and if the patients with CVD differs from patients without CVD regarding the mentioned factors above.

Subjects and methods: In 2006, 357 adult heterozygous FH patients attended visit 1 (V1). Data on medical treatment, diet and lifestyle and preferences towards the treatment was collected through an ordinary medical examination, the patient's journals and by three forms. Median one year after V1, visit 2 (V2) was conducted with 332 patients. In 2014, visit 3 (V3) part I was conducted with 64 patients, and during 2016 V3 part II was conducted with 92 patients. Data on V2 and V3 was collected according to V1, with exception of the patient preference form that was not included at V2. First, we described the state at V3. Second, we compared the data at the three visits in order to investigate any changes and trends over time. Lastly, we have compared patients with and without CVD at V3 in order to generate hypothesis regarding premature CVD among FH-patients.

Results: Total cholesterol (TC) and LDL-C improved from the pre-treatment levels to V1, and improved further from V1 to V3. Despite an aggressive LLT only 40% achieved an LDL-C <2.5 mmol/L at V3. Further, only 6.3% of those with the more stringent LDL-C goal of <1.8 mmol/L reached it. An important finding was that a number of patients developed traits of metabolic syndrome with increased fasting glucose, HbA1c and triglycerides (TG), weight, body mass index and waist circumference during the study-period. Further, adverse effects of statin and/or colesevelam therapy were reported as a problem for at least 30% of the patients. Adverse effects were also a common reason for being off statin therapy among those 13 patients who had stopped taking statin. When comparing the CVD group with the non-CVD group, we found significant differences in the risk factors age, male gender, pre-treatment TC, former smokers, waist circumference, TG, fasting glucose, HbA1c, and occurrence of metabolic syndrome. Also, patients with CVD were diagnosed with FH later in life.

Conclusion: Aggressive LLT in a highly specialized outpatient lipid clinic resulted in changes towards a more favorable cholesterol profile kept over a long time period of eight to ten years. Still, a larger part does not reach the treatment target. Further, we observed an unfavorable trend towards a more metabolic profile among the patients. When investigating if there were any differences between the patients with and without CVD, we found a higher proportion with metabolic syndrome and former smokers, and indication of a higher cholesterol burden due to late start of statin treatment among patients with CVD.

Acknowledgements

The present work has been conducted from January 2016 to November 2016 at the Lipid Clinic, Rikshospitalet, Oslo University Hospital and the Department of Nutrition, Faculty of Medicine, University of Oslo.

First of all, I would like to sincerely thank my supervisors Kjell-Erik Arnesen and Kjetil Retterstøl. Kjell-Erik for your support, guidance and encouragement during the data collection, and for letting me being involved in the working-environment at the Lipid Clinic. Kjetil for your good advices and valuable discussions during the writing process, and for always being available. You are both unique experts in the cholesterol-field and I have appreciated having you as supervisors. Thanks for everything you have taught me!

Further, a special thanks to Marlene Thorvall, for having done such a good work with the data material before me, and for your valuable help in the initial phase. And further to Marit Veierød, thanks for good advice with the statistical analysis.

I am also very thankful to my classmates for sharing frustrations and tips for how to make the best of everyday life as a master student, and off course all the coffee making and lunches during these five years.

Last but not least, a special thanks to family, friends and my dear Edvard, for your support, caring and distractions when I needed it the most.

Oslo/Averøy, November 2016

Irene Mork

Table of contents

List of abbreviations

AMI	Acute myocardial infarction
AP	Angina pectoris
Apo	Apolipoprotein
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ApoB/ApoA1	ApoB/ApoA1-ratio
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CM	Chylomicrons
CVD	Cardiovascular disease
CV	Cardiovascular
DLNC	Dutch Lipid Network Criteria
DM	Diabetes mellitus
DMT1	Diabetes mellitus type 1
DMT2	Diabetes mellitus type 2
FH	Familial hypercholesterolemia
GP	General practitioner
HDL-C	High-density lipoprotein-cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
IDL	Intermediate density lipoprotein
IDF	International Diabetes Federation
LDL-C	Low-density lipoprotein-cholesterol

LDL-R	Low-density lipoprotein-receptor
Lp(a)	Lipoprotein little a
LLM	Lipid lowering medication
MeDiet	Mediterranean diet
MetS	Metabolic syndrome
MI	Myocardial infarction
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
OUS	Oslo University Hospital
PAR	Population attributable risk
PCSK9	Proprotein convertase subtilisin/kexin type 9 protein
RCT	Randomized controlled trial
SmD	Smart Diet
TC	Total cholesterol
TG	Triglycerides
V1	Visit 1
V2	Visit 2
V3	Visit 3
VLDL	Very low-density lipoprotein
WC	Waist circumference
25-75 p	25^{th}- 75^{th} percentiles

List of tables

List of figures

List of appendices

1 Introduction

1.1 Cardiovascular disease

Cardiovascular disease (CVD) is a collective term for diseases affecting the heart and circulatory system, including coronary heart disease (CHD) such as angina pectoris (AP) and myocardial infarction (MI), and others like stroke, aneurysms and peripheral vascular disease. Globally, CVD is the number one cause of death (1). Despite decreased CVD mortality in Europe, CVD remains the most common cause of deaths with responsibility for nearly half of all deaths (2). In Norway, the age-adjusted mortality rate for CVD has declined the last four decades (3), and has now become one of the lowest age-standardized mortality rates in the European countries (2). From 2000 to 2012 the mortality rate was almost halved among men and women. The incidence rate of acute MI (AMI) for all age groups combined decreased with 24% from 2001 to 2009 (3). Apparently, the reduced mortality and AMI incidence is attributed to better primary prevention and medical treatment of CVD (3). However, an 11% increase in hospitalizations rates for AMI among younger adults from 25 to 44 years of age was observed in the same period (3). Thus, CVD is still a major public health problem (4). CVDs can largely be prevented by managing risk factors like hyperlipidemia, diabetes mellitus (DM), hypertension and obesity with medical and lifestyle interventions. Early detection and management of risk factors is necessary to prevent early disease, especially among those at high risk (1).

1.2 Lipoprotein metabolism and atherosclerosis

The lipoprotein metabolism and the atherosclerotic process is rather complex, thus this gives only a brief introduction to these themes. Plasma lipoproteins contain mainly cholesteryl esters and triglycerides (TG), and are responsible for the delivery of lipids to cells and tissues. Different apolipoproteins (apo) are bounded to the particles surface, and the composition is characteristic of each lipoprotein class. Lipoproteins are classified based on their densities determined by the relative content of lipids and proteins. In ascending order of density they are chylomicrons (CM), very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL) (5).

CM are large particles with one molecule of apoB-48, and are responsible for the transport of dietary cholesterol and fatty acids from the gut to the liver and peripheral tissues. The liver synthesizes TG and cholesterol, which along with intestinally derived lipids from CM are packed and secreted as VLDL (6). VLDL contains one molecule of apoB-100. CM and VLDL distribute energy to the peripheral tissues in the form of TG and fatty acids. In the circulation hydrolysation of TGs and fatty acids from CM and VLDL produces remnant particles like CM-remnants and IDL, respectively. CM-remnants are removed from the circulation by the liver, while IDL are subsequently converted to LDL, the predominant cholesterol-carrying particle. Thus, as VLDL, the LDL-particle also contains one single copy of apoB-100. LDL distributes cholesterol to peripheral cells, and is removed from the circulation by the LDL-receptors (LDL-R) on the surface of the hepatocytes. The apoA1-containing HDL is formed in the circulation. It is responsible for the transport of excess cholesterol from peripheral tissue to the liver for degradation and/or excretion into the bile acids, a process termed reverse cholesterol transport. HDL-cholesterol (HDL-C) can be returned to the liver either by direct uptake or through exchange of cholesteryl esters for TG in apoB-containing lipoproteins followed by hepatic uptake of apoB-containing lipoproteins (5, 6).

Atherosclerosis consists of several pathogenic events, and might eventually lead to CVDs. It is characterized by accumulation of lipids and fibrous elements followed by inflammation in the wall of large and medium-sized arteries (6). Endothelial dysfunction appears to be one of the first steps in the development of atherosclerosis. Damaged endothelium is more permeable to lipoproteins, especially LDL. Accumulation and modification, such as oxidation, of LDL in the sub-endothelial matrix recruits monocytes from the bloodstream into the arterial wall. Inside the arterial wall they differentiate to macrophages that ingests oxidized-LDL through the scavenger receptor leading to foam cell generation. Oxidized-LDL and activated macrophages stimulates the release of growth factors, cytokines and chemokines, which in turn attracts more monocytes and stimulates proliferation of intimal smooth muscle cells and fibroblasts (5).

The earliest visible lesions are fatty streaks. Over several years the fatty streaks may grow into a mature plaque, which can rupture or occlude the arterial lumen leading to thrombosis with distal ischemia. The composition of the plaque is important for the stability and the clinical consequences. A stabile plaque, characterized by a thick fibrous cap, is unlikely to rupture but can lead to stenosis. In an unstable plague the fibrous cap is thinner, the lipid core

is larger and the inflammation is more severe. This kind of plague is vulnerable, with a greater potential for rupture leading to formation of a thrombus and distal ischemia (7).

1.3 Familial hypercholesterolemia

Familial hypercholesterolemia (FH), described by the pathologist Harbitz and the internist Müller in the 1930s, is the most common genetic cause of premature CHD (8, 9). It is characterized by a severe hypercholesterolemia present from birth, which leads to about a 20-fold increased lifetime risk of CHD compared to the general population (10). Further, studies in the statin-era have shown that patients with FH still suffer from higher cardiovascular (CV) mortality than the general population (11, 12).

1.3.1 Genetics and pathophysiology

FH is an autosomal dominant disease, inherited in a heterozygous or homozygous form. It is caused by mutations in one of three genes encoding key proteins involved in the recycling pathways and functions of the LDL-R, resulting in severely elevated plasma levels of LDL-C and total cholesterol (TC) (9, 13). Patients with heterozygous FH (HeFH) have approximately a 50% reduction in function of the LDL-R (14, 15). If one parent has HeFH, there is a 50% chance of inheriting the gene mutation. Likewise, if both parents have HeFH there is in addition a 25% chance of inheriting both gene mutations and get homozygous FH (HoFH).

Most commonly affected are the genes encoding the LDL-R, where over 1700 mutations of has been discovered (16). These mutations are loss-of-function mutations, and accounts for approximately 95% of FH-cases (17). A mutation in this gene results in failure to produce LDL-R or in a reduction in the LDL-R activity, and consecutively to a reduced hepatocellular uptake of LDL-C (9, 13). Some mutations have also been found in genes encoding ApoB-100 and proprotein convertase subtilisin/kexin type 9 protein (PCSK9), but these are far less frequent than the LDL-R mutations (17, 18). ApoB-100 is required for the binding of LDL to the LDL-R. A mutation in this gene reduces the affinity for the LDL-R, and impedes the binding of the LDL, with reduced clearance of LDL-C in plasma. ApoB-100 mutations account for 2-5% of the FH-cases (17). The secreted protein PCSK9 is responsible for the degradation of LDL-R inside lysosomes in the liver cell (17). The PCSK9-mutations exist in two forms; one gain-of-function and one loss-of-function. The latter provides protection against atherosclerosis as it promotes clearance of LDL-C. In contrast, the gain-of-function

mutation decreases the number of LDL-R, and reduces the removal of plasma LDL-C. Less than 1% of FH-cases are caused by PCSK9 gain-of-function mutation (17).

1.3.2 **Prevalence and clinical manifestations**

In Norway the estimated prevalence of HeFH has generally been 1:300 (19). However, newer studies suggest a higher prevalence of 1:200 (20), implying that 25 000 people have HeFH. In comparison, only 7091 patients have genotyped FH at present, October 2016 (21), underscoring the fact that FH is severely underdiagnosed. HoFH is very rare, with an estimated prevalence of 1:1 000 000 (9). In Norway, 11 patients are diagnosed with HoFH (22), which is the double of what we could expect based on the prevalence and the population size (23).

The primary characteristic of FH is the elevated TC and LDL-C, which can be discovered in early childhood. If left untreated, adult patients with HeFH most often have TC levels in the range of 8-15 mmol/L, while HoFH have TC levels in the range of 12-30 mmol/L. HDL-C and TG levels are usually unaffected, but can be altered by obesity and insulin resistance (9, 10). In addition, physical manifestations of sustained elevations of LDL-C can become apparent with aging, and can be detected in early adulthood. These include tendon xanthomas, most common in the Achilles tendons, corneal arcus and xanthelasmas around the eyelids (13). Corneal arcus is only a sign of FH if present under 45 years of age. However, not all FH-patients develop these physical signs, and absence of any of these is not exclusive of FH (10).

Early development of CVD, such as atherosclerosis in coronary arteries and the proximal aorta, AP or MIs is typical for untreated or non-optimal treated FH-patients (13). If left untreated, CVD typically manifest in men and women with HeFH before age of 55 and 60 years, respectively. For patients with HoFH the average age at onset of CVD is 20 years (9). Patients with FH also have a high burden of asymptomatic atherosclerosis. A cross-sectional study showed that asymptomatic FH-patients had a significantly higher median total calcium score than patients with non-anginal chest pain, even though these FH-patients were treated with statins for approximately 10 years (24). A meta-analysis of carotid intima-media thickness showed that children with FH had significantly higher intima-media thickness than controls (25). It has been reported that already from eight years of age, children with HeFH has significantly greater mean carotid intima-media thickness than unaffected siblings (26).

1.3.3 **Diagnosis of FH**

A variety of diagnostic tools have been developed for clinically diagnosing FH, nevertheless a definite diagnosis can be achieved by genetic testing for the disease bearing mutations. In Europe the Dutch Lipid Clinic Network criteria (DLCN) (9) are mostly used (27). The DLCN is a set of criteria based on the patient's family history of premature CVD in their first degree relatives, their own CVD history, their untreated LDL-C, physical signs of elevated cholesterol and gene test for the causative mutations. Based on the achieved score a definite, probable or a possible diagnosis is set.

1.3.4 **Risk factors for cardiovascular disease**

FH is a CV risk factor itself due to the lifelong exposure to elevated LDL-C. In addition, patients with FH are susceptible to the same CV risk factors as the general population (28, 29). For FH-patients special importance should be given to limit all possible modifiable risk factors that confers an additionally CV risk, as the presence of one or more risk factors affects the cholesterol burden in a negative direction (9, 10).

One of the purposes of the Treat-To-Target Familial Hypercholesterolemia (TTT-FH) study was to investigate the prevalence of the CV risk factors described in the INTERHEART study, a case-control study with 11 119 cases of AMI and 13 648 controls from 52 countries. Nine risk factors accounting for over 90% of the population attributable risk (PAR) for the first AMI were identified. PAR is the reduction in incidence of a disease if the exposure where eliminated. The risk factors were elevated apoB/apoA1-ratio (apoB/apoA1), current smoking, psychosocial factors, abdominal obesity, hypertension, irregular consumption of fruits and vegetables, DM, physical inactivity and no alcohol intake (30). These are modifiable risk factors with synergistic effect on the CVD risk, and will be further described briefly. Other non-modifiable risk factors like high lipoprotein little a (lp[a]), inflammation, increasing age, male gender and familial risk will also contribute to the overall risk (31).

Elevated ApoB/ApoA1

As explained in section 1.2, ApoB and ApoA1 are proteins on the lipoproteins surface. Therefore, ApoB- and ApoA1 levels can be used as surrogate markers for the number of atherogenic particles of LDL, VLDL and remnants and anti-atherogenic HDL, respectively. An elevated TC, LDL-C and reduced HDL-C, and consecutively an elevated ApoB/ApoA1

characterize a dyslipidemic lipid profile. In the INTERHEART study an elevated ApoB/ApoA1 accounted for 49.2% of the PAR, and showed a graded relationship with no evidence of a threshold (30). ApoB/ApoA1 was the strongest predictor of MI-risk in all ages (32). According to laboratory ranges ApoB should be <0.8 g/L. For patients at great CV risk, ApoB/apoA1 is recommended to be <0.7 (33). NonHDL-C is another marker of dyslipidemia, which estimates the total number of atherogenic particles in plasma, and relates well to the apoB levels. It is recommended to be less than 3.3 mmol/L and 2.6 mmol/L for those at high CV risk and very high CV risk, respectively (27).

LDL-C

LDL-C is the concentration of cholesterol carried in LDL-particles and constitutes the major part of TC. Evidence from epidemiological (34) and Mendelian randomization studies (35) consistently shows that increased concentration of LDL-C are associated with increased risk of CVD, CHD and CVD-mortality. This is supported by evidence from randomized controlled trials (RCTs) showing that reduction of LDL-C with statin therapy reduces the risk of CVD death in both secondary and primary prevention (36, 37).

HDL-C

Currently, HDL-C role in CVD is under debate. HDL-C is the cholesterol in the HDL-particle, is inversely associated with CHD-risk in epidemiological studies (38, 39). The cardioprotective effect of HDL-C is proposed to be mediated through reverse cholesterol transport (40) as explained in section 1.2. However, Mendelian randomization studies have failed to support the causality of HDL-C observed in epidemiological studies, suggesting that HDL-C is more likely a predictor of CV risk rather than a causal factor (41, 42). Further, pharmacological increasing of HDL-C has not shown to have any beneficial effects on CVD (43). It has been suggested that a dysfunctional HDL may be more relevant than the HDL-C level (40, 44).

TG

The concentration of HDL-C and TG are inversely correlated, implicating that elevated TG might cause the increased CV risk instead of a low HDL-C. In a fasting state TGs mainly results from VLDL-particles (45). Mild-to-moderately elevated concentrations of TG, defined as 2-10 mmol/L according to Nordestgaard et al (45), are likely to induce atherosclerosis due

to the small size of the remnant particles carrying TG. This is not the case with highly elevated TG-concentrations (>50 mmol/L), where the particles are too large to accumulate in the arteries (45, 46). TGs have been shown to be an independent CV risk factor (47, 48). This is supported by genetic data (49, 50).

Lp(a)

Lp(a) is a lipoprotein containing a cholesterol rich LDL-particle, and one molecule of apoB-100 covalently bound to apo(a). Epidemiologic and genetic studies supports that elevated Lp(a) is an independent and causal risk factor for CVD (51). A large meta-analysis demonstrated a continuous association of Lp(a) levels with the CHD-risk. Adjusted for other known risk factors, the CHD-risk was increased by 13% per 3.5-fold higher Lp(a)-level (52). The exact pathogenic mechanism is not completely understood, but structural homology with plasminogen and LDL gives Lp(a) pro-thrombotic and anti-fibrinolytic activity and the possibility to accelerate atherogenesis (51).

Smoking

In the INTERHEART study, current smoking accounted for 35.7% of the PAR, and was associated with a 3-fold increase in odds of non-fatal AMI compared to never smoking. A clear dose-response relation existed between the numbers of cigarettes smoked daily and the risk of AMI (53). Smoking cessation gave a progressively fall in the MI-risk depending on the number of years since cessation and number of cigarettes smoked per day. Among light smokers (<10 cigarettes a day) the excess risk disappeared after three years of quitting. Among heavy smokers (>20 cigarettes a day) the MI-risk was still raised after 20 years or more since quitting (53).

Cigarette smoke contains several chemicals that may affect the atherosclerosis. Endothelial dysfunction and damage, increase and oxidation of pro-atherogenic lipids, decreased HDL-C, induction of inflammation and changes in the direction of a pro-coagulant state in the circulation, are thought to be the key-processes in smoking-induced atherogenesis (54-56).

Psychosocial factors

Psychosocial stress, measured as a model combining the degree of positive exposure to depression, perceived stress at home or work, low locus of control and major life events,

accounted for 28.8% of the PAR in the INTERHEART study (30). People who had experienced an AMI reported a significant higher prevalence of stress at work, stress at home, financial stress and stressful life events when compared to controls (57). Similar findings were reported after nine years follow-up in the Multiple Risk Intervention Trial. Those with three or more work stressors had a 26% increased risk of CV death (58).

Social and psychological factors have an impact on atherosclerosis and the initiation of acute cardiac events (59). Chronic stress and depression stimulates the sympathetic nervous system and hypothalamic-pituitary-adrenal axis which can lead to multiple peripheral effects like insulin resistance, endothelial dysfunction, hypertension, inflammation, platelet activation and central obesity, which all in turn promote atherosclerosis (59)

Abdominal obesity

Abdominal obesity is defined as a waist circumference (WC) >102 cm for men and >88 cm for women (31, 60), and are superior to body mass index (BMI) in discriminating obesity related cardio metabolic risk (61). In the INTERHEART study, abdominal obesity measured by WC was strongly related to the first-time MI. The highest quintile had a 77% increased MI-risk compared to the lowest quintile. Compared to the lowest quintile, WC in the highest quintile accounted for 20.9% of the PAR (30).

The accumulation of intra-abdominal fat exerts multiple metabolic effects by the excreting of adipokines and free fatty acids, leading to a an atherogenic and a pre-diabetic state (62). Additionally, abdominal obesity is associated with other CV risk factors like hypertension, dyslipidemia and DM (63, 64). Together these factors constitute the MetS; a cluster of risk factors reflecting metabolic abnormalities associated with CVD and DM type 2 (DMT2). Several different definitions of MetS exist, but all addresses the same risk factors. The National Cholesterol Education Program Adult Treatment Program (NCEP ATP) III (31) defines MetS as the presence of any three of the following five traits; WC ≥102 and 88 cm for men and women of European origin, respectively, TG ≥1.7 mmol/L or, HDL-C <1.0 mmol/L for men and 1.3 mmol/L for women, BP ≥130/85 mmHg, and fasting glucose ≥5.6 mmol/L or treatment for the latter four deviations. In the general population, MetS is associated with a 2-fold increase in CVD-risk, and a 1.5-fold increase in risk of all-cause mortality (65).

Hypertension

Hypertension is defined as systolic BP >140 mmHg or diastolic BP >90 mmHg, and is a major risk factor for CHD and stroke (66, 67). The INTERHEART study showed that hypertension accounted for 17.9% of the PAR, while the INTERSTROKE study found a PAR 37.0% of stroke (30, 68). The risk of both CHD- and stroke-related mortality increases progressively and linearly with increasing BP from 115/75 mmHg throughout middle and older age (69). Hypertension affects the endothelium lining the blood vessels, leading to endothelial dysfunction and promoting of atherosclerosis (70).

Consumption of fruit and vegetables

High consumption of fruit and vegetables was found to be a protective factor against AMI in the INTERHEART study, while low consumption accounted for 12.9% of the PAR (30). The evidence of the protective effect on CVD mainly comes from observational studies (71).Wang et al (72) reported an average risk-reduction in the CVD-mortality of 4.0% for each additional serving of fruit and vegetables combined per day, 5.0% for each serving of fruit per day and 4.0% for each serving of vegetables per day.

The cardioprotective effect can partly be explained by that a higher intake results in displacement of unhealthy food containing saturated fat and added sugar. In addition, people who consume higher amounts of fruit and vegetables tend to have a healthier lifestyle than those who consume lower amounts. Further, fruit and vegetables contains a complex mixture of vitamins, minerals, trace elements, phytochemicals and fiber which act through a variety of mechanisms leading to reduced oxidative stress, improved plasma lipid profile, lowered BP, improved insulin sensitivity and improved regulation of hemostasis (73). This complex action may explain why no supplement with single antioxidants shows benefits in primary and secondary prevention RCTs (74-76). Some RCTs have found supplementation of single antioxidants to be harmful in secondary prevention (77, 78).

Physical inactivity

Lack of physical activity accounted for 12.2% of the PAR, while regular physical activity reduced the risk of AMI with 14.0% in the INTERHEART study. The beneficial effect was noted in both genders and in younger and older individuals (30, 79). Other epidemiological studies support this inverse relationship between physical activity and CV risk (80).

Physical activity can prevent and reduce the presence of many established CV risk factors, such as elevated BP and TGs, reduced HDL-C, insulin resistance and impaired glucose tolerance, obesity (81) and inflammatory markers (82). Many of these effects are acute, and regular physical activity with moderate to high intensity should be emphasized (83).

Physical activity is also important in the secondary prevention of CHD. A Cochrane Review found a 13% reduction in total mortality and 26% reduction in CHD-mortality in patients with CHD randomized to exercise-based rehabilitation. These findings were limited to studies with a follow-up of greater than 12 months (84).

Diabetes Mellitus

DM is an endocrine disease affecting the glycemic regulation. It can either be caused by an insufficient insulin production in the endocrine pancreas, giving rise to DM type 1 (DMT1), or by a lack of ability to utilize the insulin causing DMT2. The diagnosis is based on measurement of blood glucose levels. The onset of DMT1 is acute, and is not affected by the lifestyle and diet. On the other hand, the development of DMT2 is highly influenced by the lifestyle and diet, and may develop over several years. First sign of DMT2 is insulin resistance, a preliminary stage where glucose levels are elevated but not to a sufficient extent to meet the criteria of DM (85, 86). The prevalence of DMT2 is rising, particularly driven by an increase in modifiable risk factors like physical inactivity, overweight and obesity (87).

Both DMT1 and DMT2 constitute an excess CV risk. The INTERHEART study found that DM contributed to 9.9% of the PAR. In a meta-analysis of 102 prospective studies, DM conferred about a 2-fold excess risk for CHD, major stroke subtypes and deaths due to other vascular causes, independently from other traditional risk factors. Fasting glucose levels was non-linearly related to the risk of CHD and ischemic stroke (88). Insulin resistance results in an increased lipolysis and delivery of free fatty acids from adipose tissue to the liver. This enhances the production of VLDL, and leads to an atherogenic lipid profile with elevated apoB-containing particles that drive atherosclerosis (89). Furthermore, patients with insulin resistance or DMT2 often have presence of other risk factors like hypertension, obesity and poor physical fitness that can contribute to the increased CV risk (90).

Alcohol consumption

The association between alcohol consumption and CVD is complex. The INTERHEART study found that alcohol consumption the previous year before AMI, was associated with a risk reduction of 14.0%, but this was not apparent among individuals from South-Asia (91). Excessive alcohol consumption accounted for 6.7% of the PAR (30). Observational studies associates habitual light to moderate alcohol consumption (defined as 1 and 2 drinks per day for women and men, respectively) with a decreased risk for total mortality, CV outcomes and DM compared to both non- and heavy drinkers. This also applies to patients with established CVD (92). On the other hand, excessive alcohol consumption is associated with higher risk for CV outcomes and total mortality, in a dose-depended relationship. The association is illustrated by a J-shaped curve for all outcomes (92). The protective effect is thought to be mediated through an increase in levels of HDL-C, apoA1 and adiponectin, and a reduction in fibrinogen (93). However, a recent Mendelian study found that individuals with a genetic variant associated with non-drinking and lower alcohol consumption, had a more favorable CV risk profile and a reduced CHD-risk than those without the genetic variant. The associated cardioprotective effect of light to moderate drinking in prospective studies could be explained by an elevated CV risk due to poor health in non-drinkers or by confounding of lifestyle or social factors associated with light to moderate drinking (94).

Inflammation

Prospective studies have shown that markers of inflammation may be used to predict future CV events in healthy people and in patients with CVD, where C-reactive protein (CRP), an acute phase protein and sensitive non-specific inflammation marker, is one indicator (95). In the case of CVD, it is the low-grade systemic inflammation that constitutes the risk (96). A meta-analysis of 22 studies found that CRP levels >3 mg/L was independently associated with a 60% excess risk in incident CHD compared to levels <1 mg/L (95). However, Nordestgaard et al, suggests that elevated CRP most likely is a marker for the extent of atherosclerosis or for the inflammatory activity in atherosclerotic plaques (97)

Age and gender

The risk for CVD increases progressively with age. This is a reflection of the progressive accumulation of atherosclerosis and the cumulative exposure to atherogenic risk factors (31). In CV risk scores age is crucial in determining the risk for a coronary event (98).

Male gender contributes to the CHD risk; however the potential mechanisms are not fully understood (99). The Norwegian Cardiovascular Disease Registry shows that men are seven to ten years younger than women at their first MI (100). Although the difference in risk between men and women decreases after the age of 50 years, males still have a greater risk than women throughout life. However, if a woman smokes her MI-mortality is almost the same as for a non-smoking man with the same levels of TC and BP (101).

1.3.5 **Treatment of FH**

To reduce the excess CV risk, both lifestyle improvements and lipid lowering medication (LLM) are necessary. The main principle now is to reduce LDL-C to a lower value than in the general population. The treatment is life long, and is individualized based on the LDL-C levels and presence of CV risk factors (9, 10). As LDL-C has been elevated since birth and atherosclerosis begins at an early age, early initiation of the treatment is crucial (13, 25). Due to ethical reasons, no RCTs have evaluated the effect of LLM in FH-patients, thus evidence is based on RCTs with non-FH patients or observational studies with FH-patients (102)

Treatment goals

For FH-patients without any additional CV risk, LDL-C <2.5 mmol/L is recommended, while FH-patients with DM or manifested CHD are at very high risk, a more stringent target of LDL-C <1.8 mmol/L is recommended (27). All undertreated patients with FH above age of 40 years should be considered to be at very high CV risk, as they have been exposed to elevated LDL-C for a long time. Accordingly, patients exposed to severely elevated LDL-C under age 40 will also be at great CV risk (9).

Lipid lowering medication

Statins are the first-line therapy. In need of more aggressive treatment, commonly needed in FH, ezetimibe can be added. In some cases there is a need for a third LLM, most often a resin. In addition, novel therapy as PCSK9-inhibitors is heading out (9, 10).

Statins

Statins competitively inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, the rate-limiting enzyme in the biosynthesis of cholesterol, leading to an up-regulation of the LDL-R-

synthesis and a greater uptake of LDL-C (103). Statins reduces LDL-C with 20-55% depended of type and dosage. Rosuvastatin is the most potent statin, followed by atorvastatin, simvastatin, lovastatin, pravastatin and fluvastatin. In addition, statins have a modest HDL-C rising and TG lowering effect of 5-10% and 20-40%, respectively (104). Furthermore, clinical trials have shown that statins can reduce CRP

levels up to 60% (105). In some cases, if statins are not well tolerated, extracts of red yeast rice may be used as a low potent alternative. The active ingredient Monakolin K produced by fermentation of the rice is identical to lovastatin. 10.4 mg red yeast rice lowered LDL-C with 1.02 mmol/L compared to placebo. However, safety around the use of read yeast rice has not been properly studied (106).

For each 1 mmol/L reduction in LDL-C with statin treatment, the risk of major vascular events and coronary events is reduced by 21% and 24%, respectively (36). For patients with CHD, statin therapy delays the progression and induces regression of atherosclerotic lesions (107, 108). Compared with moderate statin treatment, intensive treatment shows a greater reduction in the atherosclerotic progression (109).

Statin therapy is expected to be well tolerated by most patients. Most commonly reported adverse effects are symptoms of muscle toxicity like myopathy. Rhabdomyolysis has also been reported, a rare but serious adverse (110, 111). Further, there is an increased risk of transaminase elevations, but these are usually reversible after reduction of dose or termination of statin therapy (111). Statin therapy is also associated with an increased risk of DMT2 in non-diabetic individuals (112, 113). However, the benefit of statin treatment on CVD and mortality overweighs the increased risk of promoting DM in high-risk subjects (114).

Ezetimibe

Ezetimibe inhibits the absorption of dietary and biliary cholesterol in the small intestine. It is recommended as an additional LLM in a combination with a statin. As monotherapy, ezetimibe reduces LDL-C with 15-22% in hypercholesterolaemic patients (27, 115), and additional 15-20% in combination with a statin (116). Ezetimibe is only available in 10 mg, and is well tolerated both as monotherapy and in combination with statins (115).

In the IMPROVE-IT trial dual LLM with ezetimibe and a statin reduced LDL-C and the risk of CV events to a greater extent compared to monotherapy with a statin after six years (117). Despite achieving a reduction in LDL-C, no regression in the CIMT was observed with

ezetimibe and simvastatin compared to simvastatin in patients with FH after two years in the ENHANCE-trial (118).

Resins

Resins are bile acid sequestrates, preventing reabsorption of bile acids in the terminal ileum, and thereby blocking the enterohepatic circulation. The liver becomes depleted of bile, and increases the synthesis from hepatic cholesterol. This results in a compensatory increase in LDL-R and increased uptake of LDL-C from the circulation, which in turn reduces LDL-C levels (119). Currently, the most used resin is colesevelam, with a maximal daily dose of 3750 mg. It is often used in combination with a statin alone or a statin in addition to ezetimibe. Maximum doses lower LDL-C with approximately 20%. In combination with a statin, it gives an additive LDL-C lowering effect. HDL-C and TG levels are generally increased with treatment with colesevelam alone. In co administration with a statin the TG-increasing effect usually disappears, due to the TG-lowering effects of statins (119, 120).

Resins reduce the incidence of CV events and the progression of atherosclerotic plaques (121). In general, colesevelam is well tolerated. The most commonly reported adverse effects are gastrointestinal like flatulence, constipation, dyspepsia and sometimes diarrhea (119).

PCSK9-inhibitors

PCSK9-inhibitors are a novel treatment. They act by reducing circulatory levels of PCSK9, leading to an increased lifetime of the LDL-R and thus a reduced LDL-C. Biweekly injections leads to a 50-60% reduction in LDL-C and a 7-8% increase in HDL-C (122). Compared to placebo, treatment with PCSK9-inhibitors reduces the odds of all-cause mortality and MI with 55% and 51%, respectively (123). Currently, there are two types of PCSK9-inihibtors; evolocumab and alirocumab.

PCSK9-inhibitors can be used in combination with other LLMs in FH-patients at high risk for and/or among those who do not reach the treatment targets with maximal tolerable dosage of statin and ezetimibe (124). However, recently the Norwegian Medicine Agencies stated that PCSK9-inhibitors was only cost efficient for patients with HoFH.

Dietary and lifestyle recommendations

No conclusions about the effectiveness of a cholesterol-lowering diet in reducing CHD in FH-patients have been made due to lack of data, with exception of plant sterols and/or stanols

(125, 126). Plant sterols and stanols are components, found in small amounts in vegetable food, and compete with the cholesterol absorption in the intestine. Two gram of plant sterols daily lowers LDL-C with 8-10% (127). Nevertheless, dietary adjustments towards a cardioprotective diet are an important adjunctive treatment of FH (10, 27). The main principle is restriction of type and amount of fat (128), which can reduce LDL-C up to 30% (129). Replacing saturated fat with unsaturated fat reduces the occurrence of CVD (130, 131). An intake of 25-35 g total fat, <7% saturated fat and <1% trans-fat is recommended (128, 132, 133). This can be achieved by choosing low fat dairy products daily, lean and fatty fish two to three times weekly, four to five handfuls of unsalted nuts weekly, using vegetable oils in cooking except palm- and coconut oils, use avocados, olives, mayonnaise or oil-based spreads and dressings, and limit the intake of fatty and processed meats (134, 135). Dietary cholesterol can increase cholesterol levels to a varying degree, and patients with FH are recommended to limit the intake of dietary cholesterol to 200 mg/day. Thus, the intake of egg yolks should be moderate (two in a weekly basis) and the intake of liver and food made of animal blood and roe should be limited (135).

Further, it is recommended to have a intake of fiber greater than 25 g daily, as fiber has a hypocholesterolemic effect due to binding of bile acids in the gastrointestinal tract and preventing reabsorption from the terminal ileum (128, 136) This can be achieved by eating wholegrain products, legumes, five portions of fruit, vegetables and berries daily (137).

The intake of certain foods should be limited. Sugar-sweetened beverages and foods are energy dense, and can contribute to an excessive intake of calories and weight gain, and thus affect cholesterol levels in a negative direction. Further, they also has a TG-increasing effect (134). Foods with a high sodium-content should be limited, as a high intake of sodium is associated with elevated BP (134). Patients are newer encouraged to consume alcohol. If elevated TG is presents, patients are advised to reduce the intake to a minimum or to abstain. Overweight or obese individuals should not exaggerate the alcohol consumption, due to a high caloric content that can contribute to an excessive energy intake (132).

Many of the dietary recommendations above are achieved with the Mediterranean diet (MeDiet) (138). Already in the 1960s the Seven Countries Study associated the MeDiet with decreased CHD (139). Moreover, the MeDiet has shown beneficial effects in both primary and secondary prevention of CVD (140, 141). In the PREDIMED study, energy-unrestricted MeDiet supplemented with either extra-virgin olive oil or nuts resulted in a relative risk

reduction of 30% in major CV events among high-risk persons without CVD. In the Lyon Diet Heart Study the MeDiet lowered the rate of recurrent CVD with approximately 12% compared to the prudent Western diet (140). Several meta-analyses have confirmed the CV benefits of the MeDiet (138, 142).

When it comes to lifestyle recommendations, FH-patients are recommended to be physical active for at least 150 minutes with a moderate intensity, or 75 minutes with high/vigorous intensity at a weekly basis. Increased amounts will provide further benefits. Sedentary behavior should be limited (137). Both endurance and resistance training with moderate to high intensity is beneficial (143, 144). Additionally, physical activity affects the energy expenditure and is crucial for the energy balance and weight control (145). If presence of obesity, a 5-10% weight loss have favorable effects on metabolic and CV risk factors, particularly BP, glucose control and dyslipidemia. It is associated with a 15% reduction in LDL-C, 20-30% reduction in TG and 8-10% increase in HDL-C (146). Smoking, both passive and active, is strongly discouraged (147). Help to smoking cessation should be offered to FH-patients who smoke, and advice to children and young adults not to start smoking is important (9).

1.4 Gaps in the knowledge about FH

Although the effectiveness of LLMs are confirmed in non-FH patients with respect to hard outcomes like death and CVD, and extensive research shows the beneficial effects of a cardioprotective diet and lifestyle, there is sparse information about what is achievable in FH-patients in terms of lipid levels, diet and lifestyle in a free living outpatient clinical setting in the statin-era before PCSK9-inhibitors were available. New data shows that CVD morbidity and mortality is still higher than in the general population despite treatment (11, 12). In order to sharpen the treatment of FH to withstand future CVD, it is important to know where the treatment has potential for improvement and what might are the main driving forces of the premature CVD. This study was implemented in the pre-PCSK9-era and could be considered as what we can achieve with our traditional aggressive lipid lowering treatment. This will be crucial for the future clinical use of PCKS9-inhibitors and their cost-effectiveness and future role in the treatment of FH.

2 Aim of the study

2.1 Thesis rationale

The TTT-FH study is a prospective study of the treatment of FH given at the Lipid Clinic, Rikshospitalet, Oslo University Hospital (OUS). This thesis aims to increase the number of participants and continue the observation of effects from aggressive lipid lowering treatment in an outpatient setting over eight to ten years, started in thesis by Marlene Thorvall (148). First, we describe the present state at visit 3 (V3) regarding lipids and other blood parameters, to what extent the patients achieves LDL-C treatment targets, medications, adverse effects, patients off statin therapy, dietary and lifestyle factors and how the patients values a low cholesterol level, adverse effects, lifestyle improvement and medications.. Second, we investigate if there have been any changes regarding lipids and blood parameters, achievement of LDL-C targets, dietary and lifestyle factors and the valuing of cholesterol levels, adverse effects, lifestyle improvement and medications. Last, we describe the occurrence of CVD prior to V3 and among deceased patients, and investigate if there were any differences between patients with and without CVD at V3, focusing on lipids and other blood parameters, medication, occurrence of comorbidities, dietary and lifestyle factors.

2.2 Thesis objectives

Specific objectives in this thesis are:

1. Describe the FH-population at V3 regarding:
    a. Age at FH-diagnosis.
    b. Type and intensity of the LLM, use of antihypertensive and glucose lowering medication.
    c. Prevalence of adverse effects related to LLM.
    d. Describe the FH-patients off statin therapy regarding gender, reasons for not using statins, lipid values and CV events.
    e. Lipid levels and achievement of treatment targets.
    f. Levels of fasting glucose and HbA1c.
    g. Occurrence of abdominal obesity and metabolic syndrome (MetS).
    h. Diet and lifestyle factors like physical activity, smoking and alcohol intake.

i. Examine the patients preferences towards
    i. A healthy lifestyle relative to medical treatment.
    ii. As low cholesterol level as possible
    iii. A low cholesterol level relative to accepting having adverse effects.

2. Measure changes from V1 to V3 resulting from aggressive lipid lowering treatment concerning:
    a. Lipid levels, fasting glucose and HbA1c.
    b. BMI, weight and WC.
    c. Diet and lifestyle factors like physical activity, smoking and alcohol intake.
    d. The patients preferences towards
        i. A healthy lifestyle relative to medical treatment.
        ii. As low cholesterol level as possible.
        iii. A low cholesterol level relative to accepting having adverse effects.
3. Measure if there are differences between patients with and without CVD at V3, concerning:
    a. Age at FH-diagnosis and age at V3.
    b. Type and intensity of LLM, use of antihypertensive and glucose lowering medication
    c. Pre-treatment cholesterol levels and cholesterol levels and metabolic blood parameters at V3.
    d. BMI, weight and WC.
    e. Occurrence of abdominal obesity and metabolic syndrome.
    f. Diet and lifestyle factors like smoking, alcohol intake, and physical activity.

2.3 Hypothesis

We hypothesize that aggressive lipid lowering treatment over eight to ten years, results in a further reduction in cholesterol levels, favorable trends concerning diet and lifestyle, body weight, WC and glycemic control. Further, we hypothesize that patients with CVD at V3 has a higher burden of CV risk factors than patients free from CVD at V3.

3 Subjects and methods

3.1 Implementation of the study

From 9th of January 2006 to 9th of July 2006, 426 patients above 18 years, with definite, probably or possible FH verified by the DLCN (appendix 1) or genetic verified FH were consecutively invited to participate in the TTT-FH study. Genotyping was performed at the Department of Medical Genetics, OUS. The study was intended to be a quality assessment of the treatment at the Lipid Clinic, thus no approval by the Regional Ethical Committee for Medical Research was needed at that time. Patients who participated in other clinical trials were not invited to participate, as well as those who received LDL apheresis, were off LLM due to pregnancy, breastfeeding or other reasons, or were not able to fill out the questionnaires. Of the 426 invited patients, 357 agreed to attend visit 1 (V1). Of the excluded patients, 43 did not wish to or could not participate and 26 did not meet the inclusion criteria. Data were collected by three forms; the doctors' form (appendix 2), SmD (appendix 3) and the patient's preference form (appendix 4), which are further described in section 3.2.1. The doctors filled out the first form during the consultation, while the patients filled out the two latter upon arrival at the Lipid Clinic. Fasting blood samples were routinely drawn during two weeks prior to the consultation or shortly after, if missing. The doctor mostly measured anthropometric data during the consultation, but for a few patients these data are self-reported. Some patients had a separate consultation with a clinical dietician. Medical records was written and documented in the patient's journals.

Median one year after V1, Visit 2 (V2) was conducted. All patients included at V1 were routinely invited to a new consultation. 332 of the 357 patients continued in the study. Of the 25 excluded patients, 13 did not wish to or could not participate, seven did not meet for the consultation and five did not meet the inclusion criteria. Data was collected by the same procedure as V1, except the patient's preference form, which was not included.

The first 100 patients were invited to V3 part I in the fall of 2014. Of these, two were dead and 78 were still registered as a patient at the Lipid Clinic. They were invited by ordinary paper mail. The 20 patients, who no longer were registered as a patient, were telephoned and invited to participate in the study. A total of 67 patients completed the consultations, and 64 were included in the analysis. Of the 36 excluded patients, 25 did not wish to attend, could not

participate or was not reach, seven did not meet for the scheduled consultation and four did not meet the inclusions criteria. Data was collected by the same procedure as for V1 except for the SmD, which was reviewed and evaluated in a separate consultation with a master student in clinical nutrition. Results were published in May 2015 as the master thesis "Treat To Target Familial Hypercholesterolemia - A prospective study on effects from maximal high intensive treatment of FH patients during eight years" by Marlene Thorvall (148).

The remaining 265 patients from V2 and 25 patients from V1 formed the basis for V3 part II. The invitation was based on the waiting list at the Lipid Clinic, where the patients scheduled for a consultation from 15th of March 2015 to 30th of May 2016 were invited to further participate upon arrival at the Lipid Clinic. In addition, 13 patients on the waiting list for the autumn of 2016 were invited by phone and offered an earlier consultation; of these three declined and four was not reached. A total of 92 patients were included. Of the 197 remaining patients, ten were dead, two did not show up, two did not meet the inclusion criteria, two was overlooked when they met to their routine consultation, 55 was on the waiting list for the second half of 2016, 2017 and 2018, 13 were participating in another projects, and 113 were no longer registered as a patient at the Lipid Clinic. Data was collected by the same procedure as for V3 part I with a new master student in clinical nutrition. 38 patients did not receive a consultation with the master student. Due to sampling errors 31 patients did not receive the patient's preference form, and 12 patients answered the most recent reviewed version of SmD. In total 156 patients of the 357 patients from V1 completed V3. During the study-period of eight to ten years, the patients were scheduled for their annual consultations as FH-patients at the Lipid Clinic. **Figure 1** shows the implementation of TTT-FH study.

3.2 Materials

3.2.1 Data collection

At V1 and V2, all doctors at the Lipid Clinic participated in the data collection by following the same protocol. At V3 part I and part II, one doctor held the majority of the consultations together with a master student in clinical nutrition at each part. Between the two parts the master students coordinated themselves to ensure that the data collection occurred in the same way. An overview of a typical consultation is shown in **Figure 2**. Missing information in the forms was collected from the patient's journal to the furthest extent.

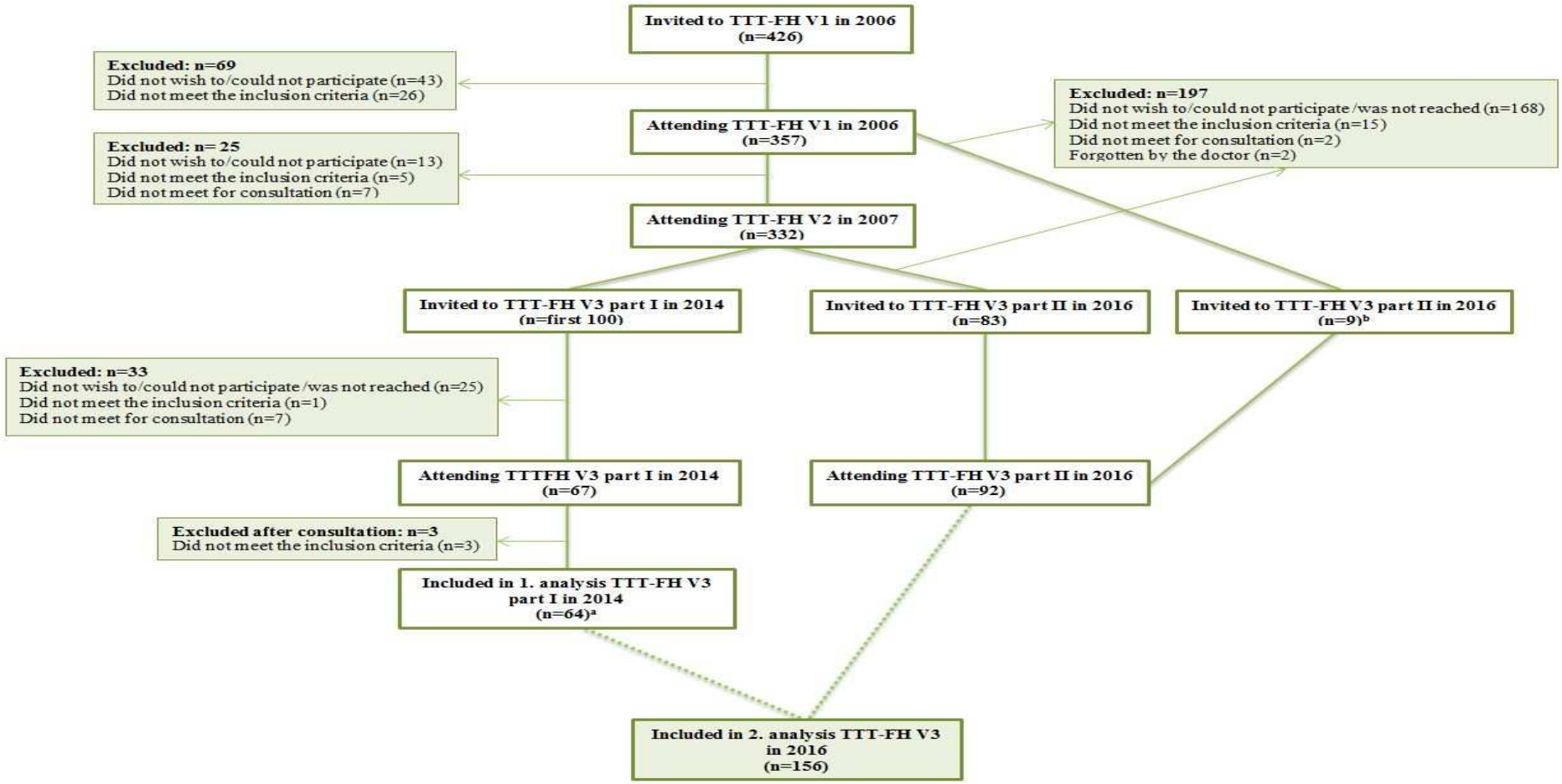

Figure 1. Flowchart - Overview of the implementation of the TTT-FH study.

[a]Presented as master thesis by Marlene Thorvall "Treat To Target Familial Hypercholesterolemia - A prospective study on effects from maximal high intensive treatment of FH patients during eight years".

[b]These patients did not attend V2.

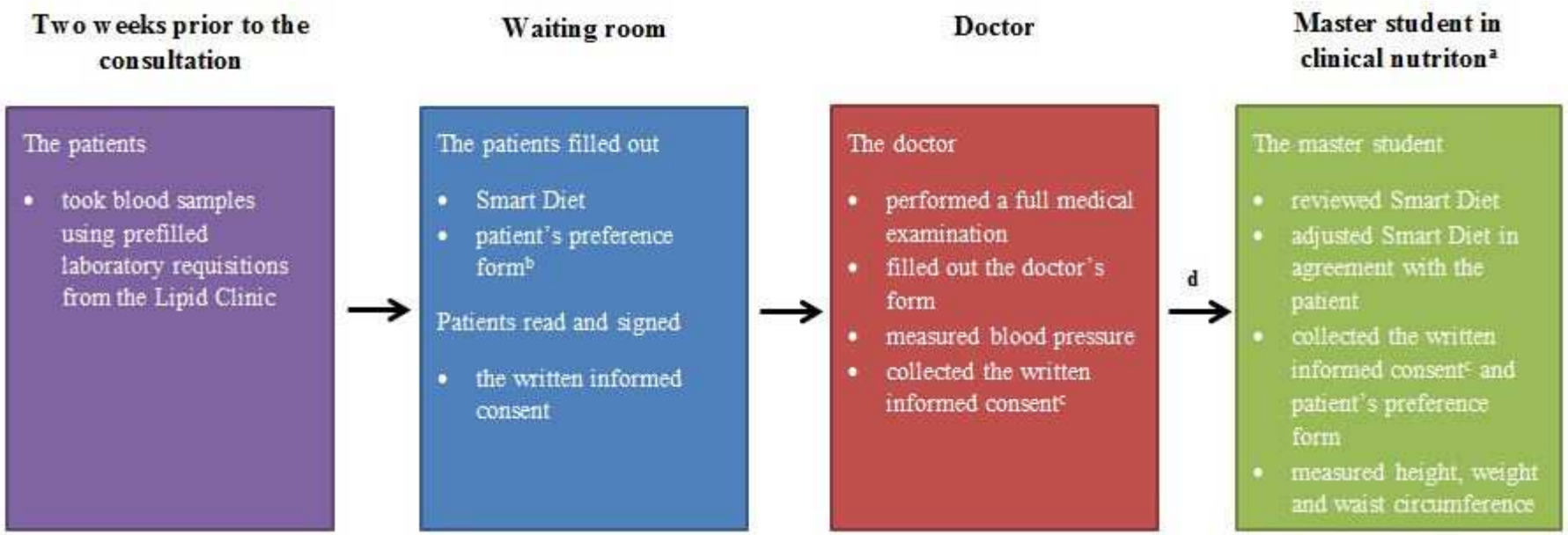

Figure 2. Illustration of a typical consultation in TTT-FH study at the Lipid Clinic, Oslo University Hospital.

[a]The master students did not attended V1 and V2. Some patients had a consultation with a clinical dietician, while other only met the doctor.

[b]The patient's preference form was not included at V2.

[c]The collection of the written informed contest was done by the health professional holding the first consultation.

[d]Sometimes the consultation with the doctor had the last consultation.

Assay methods

Most patients used a prefilled laboratory. Fasting blood samples were drawn and centrifuged within two hours of admission. The majority of the blood samples were analyzed at the Department of Medical Biochemistry, Rikshospitalet, OUS, but a few were analyzed at local laboratories. The following assay methods apply to the blood analyzed at the Department of Medical Biochemistry. Plasma (P)-TC and P-TG was measured with an enzymatic colorimetric assay, while P-LDL-C and P-HDL-C was measured with a homogeneous enzymatic colorimetric assay. P-CRP was measured by particle reinforced immunoturbidimetric assay and serum-glucose was measured enzymatic with hexokinase. All analyses were carried out on Cobes 8000, c702. ApoA1 and ApoB were measured by turbidometry on Cobas c501. The instruments, reagents and calibrator were delivered from Roche Diagnostics (Mannheim, Germany). All analyzes except LDL-C were accredited after International and European standard NS-EN ISO 15189. The laboratory results for TC, LDL-C, HDL-C, TG, apoB, apoA1, CRP, fasting glucose and HbA1c at each visit were obtained from the journals. The master students calculated ApoB/apoA1 and nonHDL-C. Untreated TC and LDL-C was mostly collected from the admission documents from their general practitioner (GP), but some were also harvested from blood drawn at the Lipid Clinic at the first consultation. Friedewalds formula (149) was used to calculate LDL-C in those cases where only TC, HDL-C and TG were analyzed. Treatment targets for FH-patients are based on guidelines from the European Atherosclerosis Society (9).

At V3 part II, BP was measured by a digital BP device of the brand Welch Allyn® Vital Signs Monitor 300 series (Welch Allyn, USA), after the patients had lied down for five minutes. It was measured three times with three minute's intervals. The last measurement was reported. At the other visits BP was measured with other, but calibrated digital BP devices.

At V3, either the doctor or the master student measured anthropometric data with the same equipment. In addition to measure weight and height as a part of SmD, WC was measured and BMI calculated. Weight was measured by an electronic body weight, Soehnle® 7720 SR 20 2763 (Soehnle, Germany). The patients were weighed without shoes, belts and heavy jewellery and with light clothing. Height was measured by a stadiometer, Seca® 222 (Seca, United Kingdom). The patients stood straight against the wall scale with heels touching the wall. BMI was calculated by dividing weight in kg by height in squared meters. WC was

measured with a non-stretchable tape over the unclothed abdomen in the middle between the lower rib and the upper part of the iliac crest, while the patient was standing and breathing calmly (150).

Medication, adverse effects and potential endpoints

The doctor's form was developed in 2006 for this study. It was revised before V3 part II, in order to obtain information on the patient's prior LLM and alterations in the treatment at V3. The doctor filled out most of the form during the consultation, but some information was obtained from the patient's journals after the consultation.

The form consists of five pages. The first page described type, intensity and duration of medications, possible adverse effects from the LLM used at V3, and if the doctor made some alterations in medication and any reasons to. Adverse effects were classified by the doctor as definite, probable or possible. An adverse effect was definite if it disappeared with discontinuation of the medication, and reoccurred with initiation of the medication. This retesting was often done several times over the years for different doses and statins, resulting in a definite impression of both the patient and the doctor of an adverse effect. An adverse effect was classified as probable if it was somewhat less certainty than above. If there was uncertainty about the relation of the adverse effect to the LLM, it was classified as possible. They were categorized based on which organ system they affected. Flatulence, diarrhea, constipation and stomach pains were categorized as gastrointestinal adverse effects. Adverse effects affecting skeleton muscles were muscle pain, muscle stiffness and asthenia. Neurological adverse effects were headache, wilt and numbness, while sexual problems were impaired erection. Malaise was classified as general adverse effects, and anxiety, nervousness and depression as psychological. Adverse effects giving dyssomnia and skin changes were classified as sleeping and skin problems, respectively. The second page dealt with any long interruptions in the LLM, when the patient first was listed as a patient at the Lipid Clinic, previous LLM, and whether the patient no longer was registered as a patient and reasons to. The date for the patient's first-time appointment at the Lipid Clinic was used as a surrogate for when the patient was clinically diagnosed with FH. The third page addressed if there had been any adverse events since last visit. Page four was partly complementary to SmD and provided information about social status and lifestyle. The last page addressed if there had been any CV endpoints such as AMI, death, coronary revascularization procedure like coronary artery bypass grafting or percutaneous coronary intervention, documented AP,

hospitalization with primary diagnosis of congestive heart failure, cerebrovascular event, first diagnosis of peripheral vascular disease, hospitalized due to peripheral vascular disease, other non-CHD vascular events or death. In addition, other CV conditions of interest were registered. These were plaque in the carotid or surrounding arteries, carotid stenosis, aorta stenosis, aorta aneurysm and implantation of cardiac ventiles or pacemaker. In addition, pharmacological treatment for hypertension and DM was collected. The diagnosis of metabolic syndrome was based on both definitions from the International Diabetes Federation (IDF) (151) and NCEP ATP III (31). The IDF criteria requires the presence of WC >94 cm and >80 cm for men and women of Caucasian origin, respectively, in addition to any two of TG ≥1.7 mmol/L, HDL-C <1.0 mmol/L in males and <1.3 mmol/L in females, systolic BP >130 mmHg or diastolic BP >85 mmHg or antihypertensive treatment, FPG ≥5.6 mmol/L or treatment of DM. NCEP ATP III requires the presence of any three of WC ≥102 cm in males and ≥88 cm in females, HDL-C <1.0 mmol/L in males and <1.3 mmol/L in females, TG ≥1.7mmol/L, BP ≥130 mmHg or diastolic BP ≥85 mmHg, FPG ≥5.6 mmol/L, or treatment for any of these deviations.

Smart Diet

Dietary and lifestyle data was collected by SmD, a questionnaire developed at the Lipid Clinic aiming to evaluate how cardioprotective the diet is. It has been used at the Lipid Clinic since 2004 (152). It is easy to use, and gives the doctor or the clinical dietician a quick overview of the patients diet, and if there is any potential for improvements. It consists of two parts where one evaluates the cardioprotective potential of the diet and the other addresses the lifestyle. In the version from 2003, the dietary part consists of 15 scoring questions with three alternatives giving one to three points. The questions are both of qualitative and quantitative. Total score gives an impression of the overall diet, while the score on the individual questions indicates whether there is potential for improvements in that area. The lifestyle component consists of five non-scoring questions, which are open for subjective assessments. SmD is self-instructive and takes about ten minutes to complete (152). Due to an improved availability of different foods and the continuously development of new products, SmD has been revised two times for adjusting the food selection, the last time was in 2009. The third revision is in progress. In addition, the number of scoring questions has been adjusted. Therefor the total score in the different SmD-versions differs. SmD is validated for all ages (153).

We used the old 2003-version of SmD during the whole study period to be able to compare the results over time. That version has a maximum score of 45 points, categorized into three categories. A total score below 29 points is defined as a low score with "potential for improvements on several areas", a total score between 30-37 points is a medium score with "potential for improvements on some areas", and 38 points or higher is a high score indicates "healthy dietary habits".

The patients filled out SmD prior to the consultations in the waiting room. Afterwards, it was used as a template for a discussion with the doctor or the dietary counseling with a clinical dietician at V1 and V2. At V3, the master student evaluated the SmD and discussed the answers with all patients. Some patients filled out the 2009-version at V3 part II. In those cases, the 2003-versions were filled out together with the master student, using the 2009 version as a template at V3. If the patient misunderstood the question or ticked wrong by a mistake, the master student corrected the answer in agreement with the patient. If the patient had ticked for more than one alternative, a mean score of was calculated. If missing answers, total score was not calculated. However, data may still be available from these patients regarding the SmD-categories if the missing value did not affect the score of the category. At V3 the master students recounted the total score from all available SmD-questionnaires from all earlier visits as a control.

Even though the version from 2003 was initially used at all visits, there are some deviations from this. At V2, 83 patients had the 2003-version, 61 patients had the 2007-version and 12 patients were missing SmD. At V3, 143 patients had the 2003-version, 12 patients had the 2009-version and one missed SmD.

To evaluate to which extent the patients had a cardioprotective diet, we made five categories out of the nine questions focusing on the food groups that form the basis of this diet; mainly low fat dairy products, lean meat and meat products, fish and fish products and fruit and vegetables.

Four questions (number 1, 2, 4 and 5) described the use of dairy products, and formed the dietary category that summed up whether the milk, sour cream and other similar varieties, cheese and butter/margarine contained high, medium or a low amount of saturated and total fat. The maximum score was 12 points. Question 11 described the use of different types of fat in cooking. Some patients who ticked off for oils might use coconut oil, which has a high

content of saturated fat. We could therefore not assume that the patients who reported that they “used oils for cooking and frying” at V1 and V2 used oils containing mostly monounsaturated fatty acids. Thus, question 11 was left out.

Question 6 and 9 described the choice of meat for dinner and cold cuts as lean, medium or fatty. These were added together and yielded a meat category with a maximum score of six points. The same applied to the fish category. Question 7 addressed how often the patient ate fish for dinner and question 10 how often the patients ate fish as cold cuts. The alternatives were quantified into “once a week or never”, “two times per week”, “three or more times per week” and “once a week or less”, “two to four times per week”, “five or more times per week”, respectively. The maximum score in the fish category was six points.

Question 12 and 13 described number of units of fruit and vegetables eaten daily. One unit was defined as one handful or approximately 150 grams. Both questions categorized the answers into “one unit or less per day”, “two units per day” or “three or more units per day”, and had a maximum score of three points. In the SmD-versions from 2007 and 2009 the questions about fruit and vegetables was merged. In order to compare the intake of fruit and vegetables across the different SmD-versions, question 12 and 13 in the 2003-version was merged to one category with a maximum score of three points. The alternatives were similar to those in the newer SmD-versions; “less than twice units a day”, “two to four units a day” and “more than four units a day”. “One unit or less per day” for both fruit and vegetable intake in the 2003-version corresponded to “less than twice units a day”. A combination of “one unit or less per day” and “two units per day” in the 2003-version corresponded to “two to four units a day”, the same did the combination of “two units per day” for both intake of fruit and vegetables and a combination of “three or more units per day” and “one unit or less per day”. A combination with “three or more units per day” and “two units per day” or “three or more units a day” in the 2003-version corresponded to “more than four units a day”.

Based on number of cigarettes smoked daily, smoking was categorized into five categories; “don’t smoke”, “five or less”, “six to ten”, “eleven or more” or “party smoker”. In addition, we merged the four latter categories into “Yes, smoker”. Alcohol consumption was categorized into “never” or how many units of alcohol consumed per week; “less than one”, “one to seven”, “eight to fourteen” or “fifteen or more”. One unit was defined as 125 mL wine, 330 mL beer or four cL spirits. Physical activity was categorized into four categories based on the number of session’s à 30 minutes or more with exercise per week; “never”, “less

than one", "once to twice" or "three or more". In addition, physical activity was categorized by intensity; "high", "moderate" or "combination of high and moderate". Endurance training and high intensity resistance training was classified as high intensity, while resistance and brisk walking was classified as moderate intensity. Use of dietary supplements was classified into "none", "cod-liver oil", "omega-3 capsules", "multivitamins" and "other". In the "other"-option, the patient could write what kind of dietary supplements that was used.

Patient's preference form

The patient's preference form is a non-validated questionnaire developed at the Lipid Clinic in 2006 for this study. It addressed to what extent the patients were satisfied with the treatment and follow-up offered at the Lipid Clinic and the patients attitudes towards different statements regarding living with FH. We choose to focus on the questions regarding diet, medication and adverse effects. The first statement is "I think that lifestyle improvements are equally important to the use of LLM". The second is if the patient wishes "his or hers cholesterol level to be as low as possible", and the third whether the patient "prefers to have little adverse effects from the medication rather than a low cholesterol level". The evaluation of all statements was divided into an ordinal scale from "fully agree", "partly agree", neither agree nor disagree", "partly disagree" to "fully disagree".

Ethics

The participation was completely voluntary. At each visit the patients read and signed a written informed consent (appendix 5) at the waiting room prior to the consultations. The doctor or the master student aimed to clarify any uncertainty regarding the study during the visit. The consents are stored in a locked room at the Lipid Clinic, where only employees has access. The Regional Ethical Committee for Medical Research gave approval of the master thesis (appendix 6).

3.3 Statistical analysis

All statistical analysis was carried out by IBM SPSS version 22.0.0.0 (SPSS Inc, Chicago). To control for plotting errors we double-checked the variables continuously during the plotting process. In addition, we double-checked ten random selected variables subsequently

in each datasheet and ran descriptive analysis. Missing data was handled by giving it a blank cell in SPSS. In case of two values for the same variable, mean was calculated.

We performed descriptive analysis of V3 and analytic analyses of the three visits. Continues variables were checked for normal distribution by inspection of histograms, normal Q-Q plots and detrended Q-Q-plots. If the continuous variables were normal distributed, mean (95% confidence interval [95% CI]) is presented. If the continuous variable were skewed median (25th -75th percentiles [25-75 p]) is presented. Categorical variables are presented as number of cases and percentages (%). In the analytic analysis, normal distributed continuous variables measured at the different visits were analyzed by a paired t-test to detect differences. If the distribution were skewed the nonparametric Wilcoxon Signed Ranks test were used. In both cases V1 was analyzed against V2, V2 against V3 and V1 against V3. For categorical variables, cross tabulation and frequency analysis was carried out. For detecting differences between two or three or more ordinal variables measured at the different visit, Wilcoxon Signed Ranks test was used. For detecting differences between two or three or more nominal variables measured at the different visit McNemars test or McNemar-Bowker test of symmetry was used, respectively. The analytic results are presented in three tables, were number of measured individuals differs due to different individuals are missing different variables at the three time-points.

We also performed analytical comparisons of patients with and without CVD at V3. Normal distributed continuous variables were analyzed by an independent t-test for detecting differences, while skewed distributed continuous variables were analyzed with the nonparametric Mann-Whitney U test. For exploring the relationship between categorical variables in the group with CVD and the group without CVD, the Chi-square test for independence was used. In cases when the assumptions of chi-square were violated, Fisher's exact two-tail probability test was used. If one of the categorical variables had more than two categories, p for trend was calculated. Missing values were handled by pairwise exclusion.

We did not conduct Bonferroni adjustment for multiple testing since this thesis mainly are a descriptive analysis with explorative p-values. A p-value <0.05 was considered statistically significant.

4 Results

4.1 Description of the FH-population at V3

4.1.1 Clinical characterization

Clinical characterizations of the study population at V3 are summarized in **table 1**. The final sample consisted of 156 patients, whereas 51.3% were males. They were middle aged and most got their clinical FH-diagnosis in their adulthood. According to their mean BMI they were slightly overweight. The vast majority had a genetically verified FH-diagnosis.

As shown in table 1, approximately one fourth and one third of the men and women, respectively, had a WC equivalent to abdominal obesity. Furthermore, around one third fulfilled the criteria of MetS set by NCEP ATP III. When using the definition set by the IDF a somewhat smaller proportion was defined as having MetS.

Nearly all patients were on statin therapy (table 1). The vast majority was treated with a high intensity statin, while a smaller portion was treated with a moderate intensity statin. In addition, the vast majority used ezetimibe in combination with a statin, except for four patients. One fourth used triple medication with colesevelam in addition to both a statin and ezetimibe. One patient used colesevelam in combination with a statin but not ezetimibe. Very few where treated with high-dose omega-3 or PCSK9-inhibitors (table 1). As much as one fifth was treated with glucose lowering drugs for DM, and approximately half of the patients were treated with antihypertensive medication. For 80 of the patients (51.3%) the LLM was changed at V3. For those who did not get their LLM intensified to maximum dosage, the following reasons were stated; patients did not wish to change their medication (9.2%), the treatment target was believed to be reached (43.4%), adverse effects (17.1%), the doctor chooses to await (2.6%), the doctor decides not to change (9.2%) and the patients was already treated with maximum LLM (18.4%) (data not shown).

Table 1. Clinical characterization of the FH-patients at V3.

Number of attending subjects at V3, n=156		
	n[a]	**%**
Male	80	51.3
Female	76	48.7
	n[a]	**Mean (95% CI)**
Age at V3, years	156	52.6 (50.6, 54.6)
Age at FH-diagnosis, years	151	33.9 (31.5, 33.4)
Height, cm		
Men	80	179.5 (178.2, 180.9)
Women	76	167.7 (166.4, 169.0)
Weight, kg		
Men	80	89.3 (85.8, 92.9)
Women	76	75.3 (71.8, 78.8)
Body mass index, kg/m^2		
Men	76	27.7 (26.6, 28.8)
Women	69	26.8 (25.5, 28.1)
Waist, cm		
Men	74	100.0 (96.9, 103.1)
Women	66	90.9 (87.5, 94.4)
	n[a]	**n (%)**
FH diagnosis[b]	156	
Genetically verified		144 (92.3)
Clinical definite		5 (3.2)
Clinical probable		3 (1.0)
Clinical possible		4 (2.6)
Cardiovascular risk factors	156	
Abdominal obesity[d]		
Men	74	26 (35.1)
Women	66	35 (53.0)
Metabolic syndrome defined by NCEP ATP III	155	47 (30.3)
Metabolic syndrome defined by the IDF	151	44 (29.1)
Medication[e]	156	143 (91.7)
High intensity statin therapy		120 (76.9)
Moderate intensity statin therapy		23 (14.7)
Hypocol		1 (0.6)
No statin therapy		13 (8.3)
Ezetimibe		123 (78.8)
Colesevelam		43 (27.6)
High dose omega-3		3 (1.9)
PCSK9-inhibitors		2 (1.3)
≥2 lipid lowering medications		119 (76.3)
≥3 lipid lowering medications		42 (26.9)
Glucose lowering medication		19 (12.2)
Antihypertensive medication		46 (29.5)

Data are given as mean (95% CI) or number of patients (%).

[a]Indicates total number of measured subjects.

[b]Verified by genotyping at Department of Medical Genetics, OUS or the DLNC

[c]Abdominal obesity is defined as a waist circumference >102 cm for men and >88 cm for women.

[d]High intensity statin therapy: atorvastatin 40-80 mg, rosuvastatin 20-40 mg. Moderate intensity statin therapy: atorvastatin 10-20 mg, rosuvastatin 5-10 mg, pravastatin 40-80 mg, simvastatin 20-40 mg, lovastatin 40 mg, fluvastatin 40 mg, pitvastatin 2-4 mg. Hypocol is red yeast rice, a nature preparate classified as a medical drug due to the small content of naturally occurring monakoliner. Ezetimibe dose was 10 mg used by 100%. Maximum colesevelam dose was 4375 mg, used by23.3%. ≥2 lipid lowering medications: least a statin and ezetimibe, ≥3 lipid lowering medications: least a statin, ezetimibe and colesevelam.

V3 *Visit 3,* FH *Familial Hypercholesterolemia,* NCEP ATP III *National Cholesterol Education Program Adult Treatment Panel III*, IDF *International Diabetes Federation, PCSK9 proprotein subtilisin/kexin type 9,* OUS *Oslo University Hospital.*

4.1.2 **Adverse effects**

An overview of the adverse effects is presented in **table 2**. Adverse effects were only reported from current used medication at V3, and either statins or resins were mostly reported as the cause. Approximately one third of those treated with statins experienced adverse effects, which mostly was muscular complaints. Also, one third of the patients treated with colesevelam experienced adverse effects, where all were gastrointestinal complaints. Of those treated with PCSK9-inhibitors or high dose omega-3, no one reported adverse effects.

Table 2. Adverse effects from lipid lowering medication used at V3.

	Statins		**Ezetimibe**		**Colesevelam**	
	n	**%**	**n**	**%**	**n**	**%**
Number using the medication	144		123		40	
No adverse effects	96	66.7	122	99.2	28	70.0
Adverse effect[a]	48	33.3	1	0.8	12	30.0
Definite	*9*	*6.3*	-	-	*3*	*7.5*
Probable	*28*	*19.4*	*1*	*0.8*	*8*	*20.0*
Possible	*11*	*7.6*	-	-	*1*	*2.5*
Type adverse effect						
Muscular	38	79.1	-	-		-
Gastrointestinal	6	12.5	1	100.0	12	100.0
Neurological	3	6.3	-	-		-
Potency/sexual problems	1	2.1	-	-		-

Data are given as number (%).

[a]Definite: the adverse effect disappeared with discontinuation of the medication and reoccurred with initiation of the medication. Probable: somewhat less security than with the definite adverse effect. Possible: some uncertainty about the relation of the adverse effect to the lipid lowering medication.

Two patients used high dose omega-3 and two patients used PCSK9-inhibitors, whereas no one reported adverse effects.

4.1.3 **Patients off statin therapy**

13 patients (8.3%) were off statin therapy and for eight of them adverse events or scepsism toward statins were reported as reasons for not using statins. Characterization of these patients is presented in **table 3.** Their TC ranged from 5.2 to 12.0 mmol/L. Accordingly, LDL-C ranged from 2.9 to 9.4 mmol/L and none of the patients reached the LDL-C treatment target. Only three patients (23.1%) were men. Four patients (2.6%) used ezetimibe as monotherapy and one patient (0.6%) used hypocol. Three patients had established CVD. Two patients had hypothyroidism, and were treated with thyroid hormones. One of them was also rheumatic, which increases the CV risk (154, 155).

Table 3. Characterization of the 13 patients off statin therapy at V3.

	Gender	Lipid lowering medication	TC, *mmol/L*	LDL-C, *mmol/L*	CVD	Other diseases	Reason for not using statins
P1	F	-	10.5	7.2	-	-	Adverse effects of statins, prefers herbal medicine.
P2	F	-	9.6	7.2	AP, PCI	HT	Adverse effects of statins.
P3	F	-	7.6	6.0	-	-	Not restarted statin after pregnancy/breastfeeding.
P4	F	-	6.8	5.2	MI, AP	-	Adverse effects of statins.
P5	M	-	12.0	9.4	-	-	Skeptical towards medication, prefers herbal medicine.
P6	F	-	9.3	6.8	-	-	Adverse effects of statins.
P7	F	-	6.2	4.8	-	-	Not restarted statin after pregnancy/breastfeeding.
P8	F	-	10.4	8.2	-	-	Anexiety of adverse effects.
P9	F	-	6.5	5.0	-	-	Not renewed the prescription.
P10	M	Ezetimbe	10.4	8.6	-	-	Non-compliance, a long break from the treatment.
P11	F	Ezetimbe	10.0	6.3	-	HT, RD	Adverse effects of statins.
P12	M	Ezetimbe	7.0	5.5	-	-	Not renewed the prescription.
P13	F	Hypocol[a]	5.2	2.9	AF	-	Adverse effects of statins.

[a]Hypocol is red yeast rice, a nature preparate classified as a medical drug due to the small content of naturally occurring monakoliner.
V3 *Visit 3,* TC *total cholesterol,* LDL-C *low-density lipoprotein cholesterol,* P *patient,* CVD *cardiovascular disease, F Female,* M *Male,* AP *angina pectoris,* PCI *percutaneous coronary intervention*, MI *myocardial infarction,* AF *atrial fibrillation,* HT *Hypothyroidism,* RD *Rheumatic disease*.

4.1.4 **Blood parameters**

Pre-treatment values of TC and LDL-C were very high, as shown in table 4. Since the patients had been exposed to an elevated LDL-C since birth, and many were diagnosed late in life, they should be considered to be at very high CV risk.

Table 4. Untreated total cholesterol and LDL-cholesterol.

Lipoprotein levels		
	n[a]	**Mean (95% CI)**
TC, *mmol/L*	150	9.8 (9.5, 10.2)
LDL-C, *mmol/L*	107	7.3 (6.9, 7.7)

Data are given as mean (95%CI).

[a]Indicates total number of measured subjects.
CI *confidence interval,* TC *total cholesterol*, LDL-C *Low-density lipoprotein cholesterol*

Mean levels of TC, LDL-C, HDL-C and TG are shown in **table 5.** LDL-C lied above the recommended level of LDL-C <2.5 mmol/L. As for LDL-C, nonHDL-C was also elevated. Levels of, ApoA1 and ApoB/ApoA1 were within the recommendations, while ApoB was somewhat elevated. Fasting levels of glucose and HbA1c was slightly elevated and just within the criteria of prediabetes (85).

Table 5. Blood parameters and blood pressure V3.

Number of attending subjects at V3, n=156		
	n[a]	
TC, mmol/L	156	5.1 (4.9, 5.4)
LDL, mmol/L	156	3.2 (3.0, 3.4)
HDL, mmol/L	156	1.4 (1.4, 1.5)
TG, mmol/L	155	1.2 (1.1, 1.2)
ApoA1, g/L	155	1.5 (1.5, 1.6)
ApoB, g/L	155	1.1 (1.0, 1.1)
ApoB/ApoA1	155	0.7 (0.7, 0.8)
NonHDL-C, mmol/L	156	3.7 (3.5, 3.9)
Glucose, mmol/L	155	5.7 (5.4, 5.9)
HbA1c, %	140	5.8 (5.6, 5.9)
CRP, mg/L[¶]	154	0.7 (0.6-1.5)
Systolic BP, mmHg	141	128.2 (126.1, 130.2)
Diastolic BP, mmHg	141	76.9 (75.4, 78.4)

Data are given as mean (95% CI) with exception of [¶]CRP where median (25-75 percentiles) are given.

[a]Indicates total number of measured subjects.

Blood was drawn in a fasting state.

V3 *visit 3*, CI *confidence interval,* TC *total cholesterol*, LDL-C *Low-density lipoprotein cholesterol*, HDL-C *High-density lipoprotein cholesterol,* TG *triglycerides,* ApoA1 *apolipoprotein A1,* ApoB *Apolipoprotein B,* CRP *C-reactive protein*, BP *Blood pressure*.

As displayed in **table 6**, nearly 40% met the treatment target of LDL-C <2.5 mmol/L. Only five patients (6.3%) of the 79 patients at very high CV risk (established CVD and DM, FH-diagnosis after the age of 40) met the treatment target of LDL-C <1.8 mmol/L, in spite of aggressive lipid lowering treatment. Of these, one was treated with PCSK9-inhibitors, a high intensity statin and ezetimibe, one with maximal LLM, two with a high intensity statin and ezetimibe, and one with a moderate intensity statin. Further, these patients had SmD-scores in the top or highest part of the middle category at V3, and all was physical active at least three times a week. One had obesity, one was overweight and the reaming was normal weight. Only one of these patients was a woman, and all was diagnosed with FH above the age of 40. At V3 all patients was above 60 years of age. Pre-treatment TC levels were around 7 mmol/L for three patients and above 10 mmol/L for one patient. One patient had unknown pre-treatment cholesterol levels (data not shown).

A significantly greater proportion at a p=0.03 of patients with an LDL-C <2.5 mmol/L was treated with a high intensity statin (45%) than patients with a LDL-C >2.5 mmol/L (22%)

(data not shown). There were also several patients with two or more LLM (50%) that had LDL <2.5mmol/L compared to patients with one or none LLM (33%) (p=0.013, data not shown). No difference in the intensity of the statin therapy among those who met and did not meet the target of an LDL-C <1.8 mmol/L was observed. This was also the case regarding treatment with two or more LLMs (data not shown).

Table 6. Number of patients achieving the treatment targets at V3.

Number of attending subjects at V3, n=156		
	n[a]	**n (%)**
LDL <2.5 mmol/L[b]	156	62 (39.7)
LDL <1.8 mmol/L[b,c]	79	5 (6.3)
without PCSK9-inhibitors	*79*	*4 (5.1)*

Data are given as number (%).

[a]Indicates number of patients the target applies to.

[b]Targets are according to the guidelines from the European Atherosclerosis Society

[c]Applies to patients with CVD, DM or diagnosed later than 40 years of age.

V3 *visit 3,* LDL-C *low-density lipoprotein cholesterol,* PCSK9 *proprotein subtilisin/kexin type 9.*

4.1.5 **Dietary and lifestyle factors**

Dietary factors

The results from SmD are presented in t**able 7**. As the SmD-score indicates, the patients had a relatively cardioprotective diet. This is confirmed by the distribution of the patients in the three SmD-categories. Only a few patients had a SmD-score corresponding to the lowest category.

We evaluated SmD-subgroups of different foods. Overall, the patients had a diet consistent with our recommendations. They chose mainly low-fat dairy products, where most patients used skimmed milk, plant-based margarine and rarely used cream and similar products. However, in terms of cheese a number of patients used whole- and half-fat varieties instead of the leanest alternatives (data not shown). They achieved good SmD-scores on meat, were the main part of the patients used low fat meat for dinner and as cold cuts, but the SmD-scores on fish were less impressive. Based on the practical experience from the dietary consultation, the impression is that most patients eat fish for dinner and as sandwich filling two to four times a week. Most of the patients had a lower intake of fruit and vegetables than recommended, and no more than one third had a daily intake of four portions or more.

Evaluation of the intake of fruit and vegetables separately revealed some distortions. 30.5% and 33.3% had a daily intake of less than one portion of vegetables and fruit, respectively. This does not match the result from the category with fruit and vegetables together, where only 9.2% had an intake of less than two portions a day.

Over half of the patients used dietary supplements on a regular basis. Omega-3 capsules and cod liver oil was mostly used, while a minority used multivitamins and other supplements like B-vitamins, arginine and different antioxidants (data not shown).

Lifestyle factors

An overview over smoking, alcohol consumption and physical activity is shown in **table 8**. The majority of the patients did not smoke. Of those who were smokers, 10.3% were regular smokers, while the remaining 3.9% was period smokers, preferably at parties. Approximately 40% were former smokers.

A small percentage reported not to consume alcohol. Of those drinking alcohol, most had a moderate intake.

Half of the FH-population was physical active at least 30 minutes three times a week. Approximately 17% reported to never be physical active. Of those being physical active the majority exercised with moderate intensity or a mix between moderate and high intensity.

Table 7. Description of dietary results from Smart Diet at V3.

Number of attending subjects at V3, n=156		
	n[a]	
SmD score, p[§]	140	36.4 (35.9, 37.0)
SmD catecory[ǂ]	153	
1 (<30 p)		4 (2.6)
2 (30-37 p)		86 (56.2)
3 (>38 p)		63 (41.2)
SmD subgroups		
Dairy (4-12 p)[§]	153	10.0 (9.8, 10.3)
Meat (3-6 p)[¶]	153	6.0 (3.0-6.0)
Fish (3-6 p)[§]	153	4.0 (3.8, 4.2)
Fruit and vegetables (1-3 p)[§]	153	2.2 (2.1, 2.3)
1 (<2 portions/day)[ǂ]		*14 (9.2)*
2 (2-4 portions/day)[ǂ]		*92 (60.1)*
3 (>4 portions/day)[ǂ]		*47 (30.7)*
Vegetables (1-3 p)[§]	141	1.9 (1.8, 2.0)
1 (<1 portions/day)[ǂ]		*42 (30.5)*
2 (1-2 portions/day)[ǂ]		*69 (48.9)*
3 (>3 portions/day)[ǂ]		*3 (20.6)*
Fruit (1-3 p)[§]	141	1.9 (1.8, 2.0)
1 (<1 portions/day)[ǂ]		*47 (33.3)*
2 (1-2 portions/day)[ǂ]		*60 (42.5)*
3 (>3 portions/day)[ǂ]		*34 (24.1)*
Dietary supplements[ǂ]	147	
None		55 (37.4)
Cod-liver oil		*36 (24.5)*
ώ-3 capsules		*43 (29.3)*
Multivitamins		*20 (13.6)*
Other		*28 (19.0)*

Data are given as [§]mean (95% CI), [¶]median (25-75 percentiles) or [ǂ]number (%).

[a]Indicates total number of measured subjects.

V3 *visit 3,* SmD *Smart Diet,* p *points,* CI *Confidence interval*

Table 8. Description of lifestyle results from Smart Diet at V3.

Number of attending subjects at V3, n=156		
	n[a]	
Smoking	155	
No		133 (85.8)
Yes, number of sigarettes		22 (14.2)
≤5		*6 (3.9)*
6-10		*9 (5.8)*
≥11		*1 (0.6)*
Party smoker		*6 (3.9)*
Former smoker, years[§]	62	17.5 (14.3, 20.7)
Former smoker, number of cigarettes/day[§]	48	12.0 (9.7, 14.2)
Alcohol consumption, units a week[‡ b]	155	
0		23 (14.8)
<1		45 (29.0)
1-7		76 (48.7)
8-14		11 (7.1)
≥15		0 (0.0)
Physical activity, sessions >30 min a week[‡]	156	
Never		5 (3.2)
<1		22 (14.1)
1-2		49 (31.4)
≥3		80 (51.3)
Intensity of physical activity[‡c]	141	
High		11 (7.8)
Moderate		82 (58.2)
Mixed		44 (31.2)

Data are given as mean (95% CI) or number (%).

[a]Indicates total number of measured subjects.

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

[c]A high intensity of physical activity is equal to endurance training, a moderate intensity is equal to brisk walking and resistance training, a mixed intensity is a mixture of endurance and resistance training.

V3 *visit 3,* SD *Smart Diet,* CI *Confidence interval*

4.1.6 **Patients preferences concerning the treatment**

Figure 3a, 3b and **3c** shows how the patients value the statements "a healthy lifestyle is as important as medicines", "I want as low cholesterol level as possible" and "I prefer to have little adverse effects rather than a low cholesterol level". The majority of the patients valued the first two statements equally, while the last statement showed a more scattered valuation.

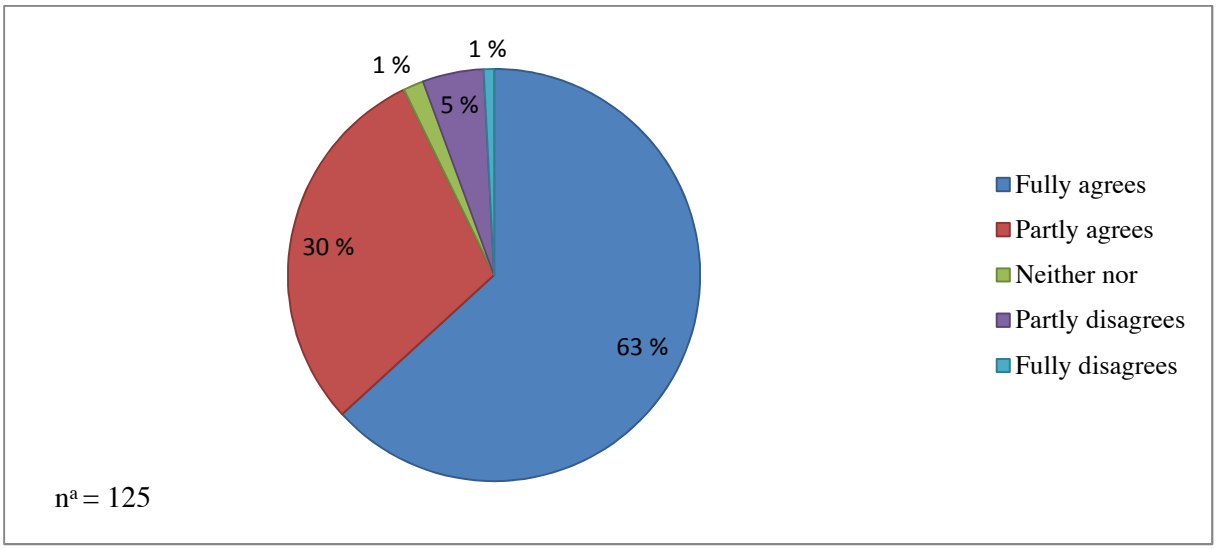

Figure 3a. Overview over how the FH-patients values the statement "I consider a healthy lifestyle as important as medical treatment" at V3.

[a]Indicates total number of measured subjects

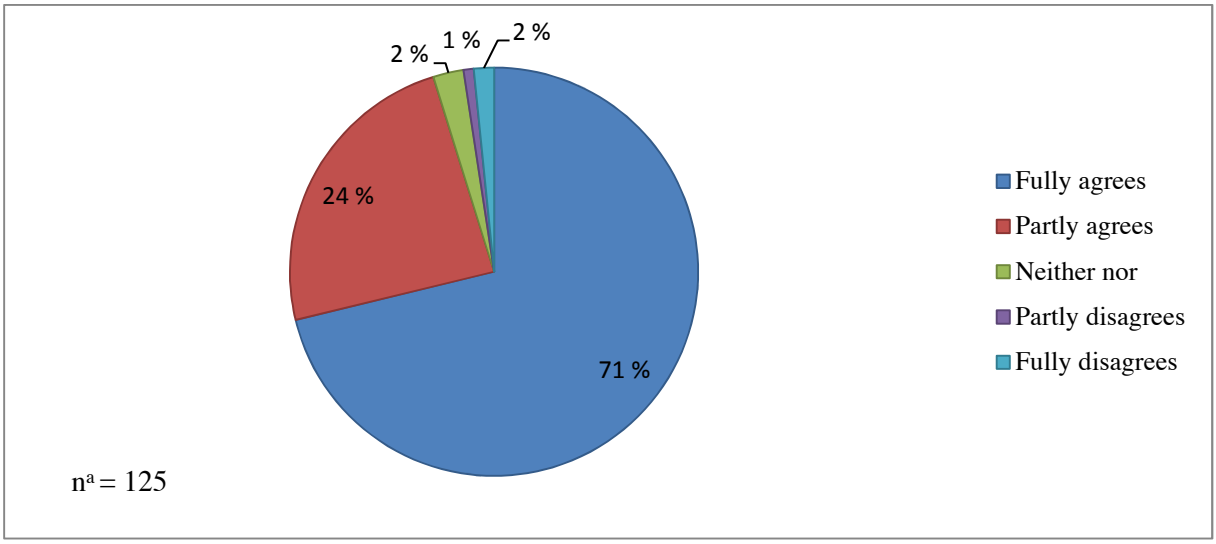

Figure 3b. Overview over how the FH-patients values the statement "I want as low cholesterol level as possible" at V3.

[a]Indicates total number of measured subjects.

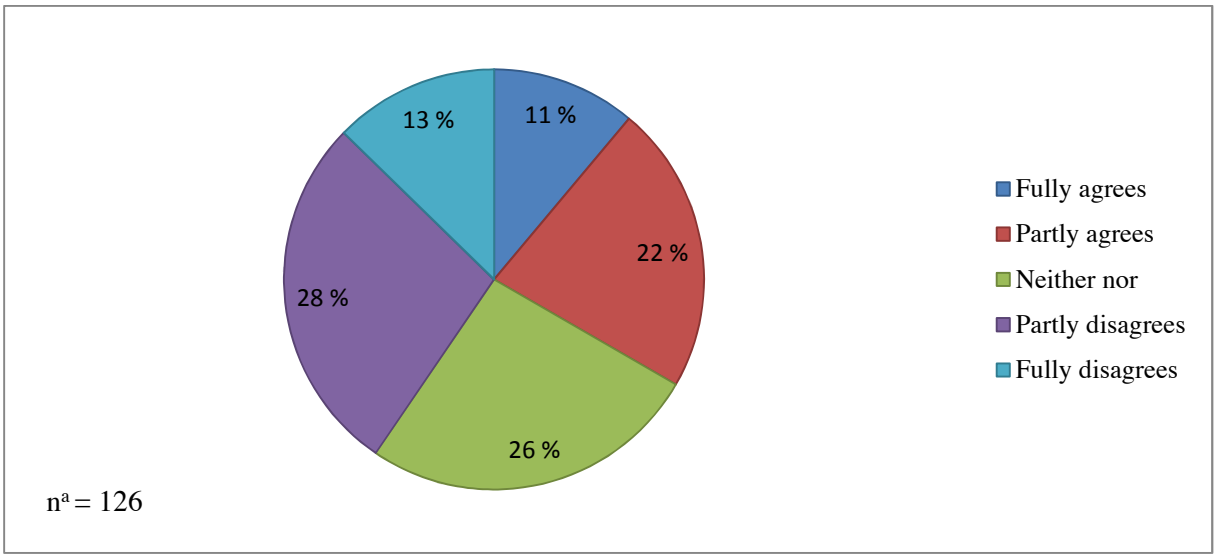

Figure 3c. Overview over how the FH-population values the statement "A low cholesterol is more important than not having adverse effects"[b] at V3.

[a]Indicates total number of measured subjects.

[b]Original statement: I prefer to have little adverse effects rather than low cholesterol

4.2 Changes in CV risk factors during eight to ten years

4.2.1 Anthropometric data

During the study period, both men and women gained weight. Consequently, we found a significant increase in BMI for both genders, and during the whole study period they were classified as overweight. WC was only significant increased among men. These results are presented in **table 9a, 9b** and **9c.**

Table 9a. Comparisons of anthropometric data of the subjects at V1 and V2.

Number of attending subjects	V1 n=156		V2 n=147		P-value
	n[a]	Mean (95% CI)	n[a]	Mean (95% CI)	
Weight, *kg*					
Men	61	88.4 (84.7, 92.1)	61	90.1 (86.1, 94.1)	0.001*
Women	61	72.5 (68.9, 76.2)	61	74.5 (70.1, 78.2)	0.002*
BMI, kg/m^2 [b]					
Men	61	27.6 (26.5, 28.7)	61	28.1 (26.9, 29.3)	0.001*
Women	61	25.8 (24.6, 27.1)	61	26.6 (25.3, 27.8)	0.002*
Waist, cm					
Men	15	96.7 (91.5, 101.9)	15	98.9 (93.0, 104.8)	0.149
Women	21	90.6 (84.5, 96.6)	21	92.9 (87.3, 98.5)	0.196

Table 9b. Comparisons of anthropometric data of the subjects at V2 and V3.

Number of attending subjects	V2 n=156		V3 n=147		P-value
	n[a]	Mean (95% CI)	n[a]	Mean (95% CI)	
Weight, *kg*					
Men	72	88.7 (85.1, 92.4)	72	90.2 (86.3, 94.0)	0.156
Women	66	74.2 (70.6, 77.7)	66	74.9 (71.4, 78.4)	0.483
BMI, kg/m^2 [b]					
Men	72	27.6 (26.5, 28.7)	72	28.1 (26.9, 29.3)	0.145
Women	66	26.4 (25.2, 27.7)	66	26.7 (25.5, 27.9)	0.500
Waist, *cm*					
Men	51	97.0 (93.5, 100.4)	51	100.8 (97.4, 104.2)	0.003*
Women	42	91.9 (87.8, 96.0)	42	92.2 (87.8, 96.6)	0.866

Table 9c. Comparisons of anthropometric data of the subjects at V1 and V3.

Number of attending subjects	V1 n=156		V3 n=156		P-value
	n[a]	Mean (95% CI)	n[a]	Mean (95% CI)	
Weight, *kg*					
Men	68	87.9 (84.5, 91.2)	68	91.0 (87.2, 94.9)	0.006*
Women	67	72.1 (68.7, 75.5)	67	74.9 (71.5, 78.4)	0.006*
BMI, kg/m^2 [b]					
Men	68	27.3 (26.3, 28.3)	68	28.3 (27.1, 29.5)	0.006*
Women	67	25.7 (24.5, 26.8)	67	26.7 (25.5, 27.9)	0.007*
Waist, *cm*					
Men	22	97.5 (92.2, 102.7)	22	103.9 (95.8, 112.1)	0.001*
Women	20	90.8 (84.7, 96.9)	20	94.4 (88.1, 100.7)	0.183

Data are given as mean (95% CI).

[a]Indicates total number of measured subjects.

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

V1 *Visit 1,* V2 *Visit 2,* V3 *Visit 3,* CI *Confidence interval,* BMI *Body mass index.*

For calculation of p-values, paired t-test was used.

*Significant change at $p<0.05$

4.2.2 **Blood parameters**

Changes in pre-treatment levels of TC and LDL-C to V1 are shown in **table** 10. Comparisons of blood parameters between V1 and V2, V2 and V3 and V1 and V3 are shown in **table 11a, 11b** and **11c**, respectively.

Despite the increased body weight, mean TC decreased from V1 (table 10) to V2 and V3. TC kept decreasing during the whole study period. The same improving trend was observed for LDL-C as for TC, but with an even stronger reduction and from V1 to V3 LDL-C was reduced with mean 0.6 mmoL/L (table 11a, b and c). The number of patients with LDL-C <2.5 mmol/L was significantly increased with 33.3% from V1 to V3 at p<0.005 (data not shown). Due to changes in the secondary treatment target during the study period, changes in the number who had an LDL-C <1.8 from V1 to V3 was not evaluated.

Table 10. Changes in pre-treatment levels of total cholesterol and LDL-cholesterol to V1.

Number of attending subjects	**Pre-treatment n=156**		**V1 n=156**				**P-value**
	n[a]	**Mean (95% CI)**	**n[a]**	**Mean (95% CI)**	**Mean change (95% CI)**	**Percent change**	
TC, mmol/L	149	9.8 (9.5, 10.2)	149	5.6 (5.4, 5.8)	-4.2 (-4.6, -3.8)	-42.9%	<0.005 *
LDL-C, mmol/L	106	7.3 (6.9, 7.7)	106	3.8 (3.6,4.1)	-3.4 (-3.9, -3.0)	-47.9%	<0.005 *

Data are given as mean (95% CI) or percent reduction.

[a]Indicates total number of measured subjects.

V1 *visit 1*, CI *confidence interval,* TC *total cholesterol*, LDL-C *Low-density lipoprotein cholesterol*.

For calculation of p-values, paired t-test was used.

*Significant change at p<0.05

HDL-C showed a small significant decline from V1 to V2; however it was significantly increased in the same manner from V2 to V3. TG showed an unfavorable trend, by increasing during the study period.

NonHDL-C followed similar development as TC and LDL-C, and was significantly reduced during the study period. Both ApoB and ApoA1 increased, and therefore no difference was observed in ApoB/ApoA1.

Glucose and HbA1c increased with 11.7% and 7.4% from V1 to V3, respectively. CRP was low during the whole study period. At all visits median value was 1.0 mg/L or lower.

Table 11a. Comparisons of blood parameters and blood pressure at V1 and V2

Number of attending subjects	V1 n=156		V2 n=147		P-value V1-V2
	n[a]	Mean (95% CI)	n[a]	Mean (95% CI)	
TC, mmol/L	145	5.6 (5.4, 5.8)	145	5.3 (5.0, 5.5)	0.002*
LDL, mmol/L	144	3.8 (3.6, 4.0)	144	3.5 (3.3, 3.7)	0.001*
HDL, mmol/L	145	1.4 (1.3, 1.4)	145	1.3 (1.3, 1.4)	0.024*
TG, mmol/L	141	1.0 (0.9, 1.1)	141	1.0 (0.9, 1.1)	0.564
ApoB, g/L	140	1.0 (0.9, 1.1)	140	1.0 (1.0, 1.1)	0.642
ApoA1, g/L	142	1.4 (1.3, 1.4)	142	1.4 (1.3, 1.4)	0.812
ApoB/ApoA1	140	0.8 (0.7, 0.8)	140	0.8 (0.7, 0.8)	0.835
NonHDL, mmol/L	145	4.2 (4.0, 4.4)	145	3.9 (3.7, 4.1)	0.006*
Blood glucose, mmol/L	130	5.1 (5.0, 5.3)	130	5.3 (5.1, 5.5)	0.056
HbA1c, %	118	5.4 (5.4, 5.5)	130	5.5 (5.4, 5.6)	0.255
CRP, mg/L[¶]	133	1.0 (0.5-1.7)	133	1.0 (0.0-1.7)	0.542
Systolic BP, mmHg	106	130.2 (127.1, 133.2)	106	127.9 (125.2, 130.6)	0.080
Diastolic BP, mmHg	105	79.1 (77.1, 81.1)	105	78.3 (76.4, 80.3)	0.376

Table 11b. Comparisons of blood parameters and blood pressure at V2 and V3

Number of attending subjects	V2 n=147		V3 n=156		P-value V2-V3
	n[a]	Mean (95% CI)	n[a]	Mean (95% CI)	
TC, mmol/L	146	5.3 (5.1, 5.5)	146	5.1 (4.8, 5.3)	0.103
LDL, mmol/L	145	3.5 (3.3, 3.7)	145	3.1 (2.9, 3.3)	0.003*
HDL, mmol/L	146	1.3 (1.3, 1.4)	146	1.4 (1.4, 1.5)	0.003*
TG, mmol/L	143	1.0 (0.9, 1.1)	143	1.2 (1.1, 1.3)	0.001*
ApoB, g/L	141	1.0 (0.9, 1.1)	141	1.1 (1.0, 1.1)	0.001*
ApoA1, g/L	143	1.4 (1.4, 1.4)	143	1.6 (1.5, 1.6)	<0.005*
ApoB/ApoA1	141	0.8 (0.7, 0.8)	141	0.7 (0.7, 0.8)	0.312
NonHDL, mmol/L	146	3.9 (3.7, 4.1)	146	3.6 (3.4, 3.9)	0.024*
Blood glucose, mmol/L	134	5.3 (5.1, 5.5)	134	5.7 (5.4, 6.0)	<0.005*
HbA1c, %	115	5.5 (5.4, 5.6)	115	5.8 (5.7, 6.0)	<0.005*
CRP, mg/L[¶]	136	1.0 (0.0-1.6)	136	0.7 (0.6-1.4)	0.758
Systolic BP, mmHg	116	121.1 (124.5, 129.6)	116	128.7 (126.3, 131.1)	0.225
Diastolic BP, mmHg	116	77.6 (75.6, 79.4)	116	76.9 (75.2, 78.7)	0.527

The table continues on the next page.

Table 11c. Comparisons of blood parameters and blood pressure at V1 and V3

Number of attending subjects	V1 n=156		V3 n=156		P-value V1-V3
	n[a]	Mean (95% CI)	n[a]	Mean (95% CI)	
TC, mmol/L	155	5.6 (5.4, 5.8)	155	5.1 (4.9, 5.4)	0.002*
LDL, mmol/L	155	3.8 (3.6, 4.0)	155	3.2 (2.9, 3.4)	<0.005*
HDL, mmol/L	155	1.4 (1.3, 1.5)	155	1.4 (1.4, 1.5)	0.137
TG, mmol/L	152	1.0 (0.9, 1.1)	152	1.2 (1.1, 1.2)	<0.005*
ApoB, g/L	152	1.0 (1.0, 1.1)	152	1.1 (1.0, 1.1)	0.010*
ApoA1, g/L	152	1.4 (1.3, 1.4)	152	1.5 (1.5, 1.6)	<0.005*
ApoB/ApoA1	152	0.8 (0.7, 0.8)	152	0.7 (0.7, 0.8)	0.443
NonHDL, mmol/L	155	4.2 (4.0, 4.4)	152	3.7 (3.5, 3.9)	0.001*
Fasting glucose, mmol/L	142	5.1 (5.0, 5.2)	142	5.7 (5.4, 6.0)	<0.005*
HbA1c, %	127	5.4 (5.4, 5.5)	127	5.8 (5.6, 5.9)	<0.005*
CRP, mg/L[¶]	146	1.0 (0.5-1.7)	146	0.7 (0.6-1.5)	0.235
Systolic BP, mmHg	114	129.4 (126.5, 132.4)	114	129.0 (126.7, 131.4)	0.796
Diastolic BP, mmHg	113	78.6 (76.7, 80.4)	113	76.9 (75.1, 78.6)	0.143

Data are given as mean (95% Cl) for all variables with exception of [¶]CRP where median (min, max) are given.
[a]Indicates total number of measured subjects.

Blood was drawn in a fasting state.
V1 *visit 1*, *V2* Visit 2, V3 *visit 3*, CI *confidence interval,* TC *total cholesterol*, HDL-C *High-density lipoprotein cholesterol*, LDL-C *Low-density lipoprotein cholesterol,* TG *triglycerides,* ApoA1 A*polipoprotein A1*, ApoB *Apolipoprotein B*, CRP *C-reactive protein*, BP *Blood pressure*.

P-values were calculated with a paired t-test, with exception of [¶]CRP where a Wilcoxon Signed rank test was used.
*Significant change at p<0.05

4.2.3 **Dietary and lifestyle factors**

Dietary factors

Multiple comparisons of the results from SmD are shown in **table 12a, 12b** and **12c**. SmD-score was significantly increased from V1 to V3. This positive trend was confirmed by changes in the distribution of the SmD-categories. The proportion with the lowest SmD-category was more than halved, and an approximately 10% increase was seen in the proportion that achieved the top category. When analyzing the SmD-subgroups, significant differences between the visits regarding intake of meat, fish, fruit and vegetables together and separately and use of omega-3 capsules was observed.

The patients had a significant higher intake of low-fat meat at V2 and V3 compared to V1, indicating that more patients chose low-fat meat for dinner and as cold cuts. There was a non-significantly reduction in the point score for fish intake from V1 to V2, but from V2 to V3 it was significantly increased. This indicates that the patients had a higher intake of fish weekly,

either with an increase in the number of times they ate fish as cold cuts/spreads, in the number of times they ate fish for dinner or a combination of those two.

The intake of fruit and vegetables together was significantly higher on V3 compared to V2, but no difference between V1 and V3 was observed. The significant increase in intake of fruit and vegetables together from V2 to V3 could be a result of the increase in intake of vegetables in the same period. At V3, the intake of vegetables alone was significantly higher than at V1 and V2. The fruit intake alone was significantly lower at V2 compared to V1 (table 12a). There were no significant difference between the fruit intake at V1 and V3, or V2 and V3 (table 12c and 12b, respectively).

The proportion who used dietary supplements at V1, V2 and V3 was stable, except for the use of omega-3 capsules, were a significantly lower proportion used them at V3 compared to V1.

Table 12a. Comparisons of dietary results from Smart Diet at V1 and V2.

Number of attending subjects		**V1 n=156**		**V2 n=147**	**P-value V1-V2**
	n[a]		**n[a]**		
SmD-score, p[§]	59	35.7 (34.6, 36.7)	59	36.4 (35.6, 37.3)	0.111
SmD-catecory[‡]	139	89.1	124	84.4	0.189
1 (<30 p)	-	9 (6.5)	-	5 (4.0)	
2 (30-37 p)	-	88 (63.3)	-	71 (57.3)	
3 (≥38 p)	-	42 (30.2)	-	48 (38.7)	
SmD-subgroups					
Dairy (4-12 p)[§]	102	10.1 (9.9, 10.4)	102	10.4 (10.1, 10.7)	0.074
Meat (3-6 p)[¶]	106	6.0 (5.0-6.0)	106	6.0 (6.0-6.0)	0.006*
Fish (3-6 p)[§]	105	3.9 (3.6, 4.1)	105	3.8 (3.6, 4.1)	0.741
Fruit and vegetables (1-3 p)[§]	105	2.1 (2.0, 2.3)	105	2.0 (1.9, 2.2)	0.170
1 (<2 portions/day)[‡]	-	*16 (15.2)*	-	*27 (25.7)*	
2 (2-4 portions/day)[‡]	-	*59 (56.2)*	-	*47 (44.8)*	
3 (>4 portions/day)[‡]	-	*30 (28.6)*	-	*31 (29.5)*	
Vegetables (1-3 p)[§]	76	1.7 (1.5, 1.8)	76	1.7 (1.5, 1.8)	0.891
1 (<1 portions/day)[‡]	-	34 (44.7)	-	*36 (47.4)*	
2 (1-2 portions/day)[‡]	-	*32 (42.1)*	-	*29 (38.1)*	
3 (≥3 portions/day)[‡]	-	*10 (13.2)*	-	*11 (14.5)*	
Fruit (1-3 p)[§]	76	1.9 (1.8, 2.2)	76	1.7 (1.5, 1.9)	0.004*
1 (<1 portions/day)[‡]	-	*25 (32.9)*	-	*37 (48.7)*	
2 (1-2 portions/day)[‡]	-	*30 (39.5)*	-	*23 (30.2)*	
3 (≥3 portions/day)[‡]	-	*21 (27.6)*	-	*16 (21.1)*	
Dietary supplements[‡]	129	82.7	134	91.2	
None	-	41 (31.8)	-	48 (35.8)	1.000
Cod-liver oil	-	*35 (27.1)*	-	*36 (26.9)*	0.286
ώ-3 capsules	-	*58 (45.0)*	-	*49 (36.6)*	0.076
Multivitamins	-	*24 (18.6)*	-	*25 (18.7)*	0.804
Other	-	*19 (14.7)*	-	*22 (16.4)*	0.791

The table continues on the next page.

Table 12b. Comparisons of dietary results from Smart Diet at V2 and V3.

Number of attending subjects		**V2 n=147**		**V3 n=156**	**P-value V2-V3**
	n[a]		**n**[a]		
SmD-score, p[§]	63	36.2 (35.4, 37.1)	63	36.5 (35.6, 37.4)	0.606
SmD-catecory[‡]	124	84.4	153	98.1	0.157
1 (<30 p)	-	5 (4.0)	-	4 (2.6)	-
2 (30-37 p)	-	71 (57.3)	-	86 (56.2)	-
3 (≥38 p)	-	48 (38.7)	-	63 (41.2)	-
SmD-subgroups					
Dairy (4-12 p)[§]	118	10.4 (10.1, 10.6)	118	10.2 (9.9, 10.4)	0.152
Meat (3-6 p)[¶]	124	6.0 (5.6-6.0)	124	6.0 (6.0-6.0)	0.876
Fish (3-6 p)[§]	124	3.8 (3.6, 4.1)	124	4.1 (3.9, 4.3)	0.024*
Fruit and vegetables (1-3 p)[§]	123	2.0 (1.9, 2.1)	123	2.2 (2.1, 2.3)	0.005*
1 (<2 portions/day)[‡]	-	*31 (25.2)*	-	*12 (9.8)*	-
2 (2-4 portions/day)[‡]	-	*60 (48.8)*	-	*71 (57.7)*	-
3 (>4 portions/day)[‡]	-	*32 (26.0)*	-	*40 (32.5)*	-
Vegetables (1-3 p)[§]	82	1.6 (1.5, 1.8)	82	1.9 (1.7, 2.0)	0.017*
1 (<1 portions/day)[‡]	-	*41 (50.0)*	-	*30 (36.6)*	-
2 (1-2 portions/day)[‡]	-	*30 (36.6)*	-	*34 (41.4)*	-
3 (≥3 portions/day)[‡]	-	*11 (13.4)*	-	*18 (22.0)*	-
Fruit (1-3 p)[§]	82	1.7 (1.6, 1.9)	82	1.9 (1.7, 2.0)	0.138
1 (<1 portions/day)[‡]	-	*38 (46.3)*	-	*29 (35.4)*	-
2 (1-2 portions/day)[‡]	-	*28 (34.1)*	-	*35 (42.6)*	-
3 (≥3 portions/day)[‡]	-	*16 (19.5)*	-	*18 (22.0)*	-
Dietary supplements[‡]	134	91.2	147	94.2	
None	-	48 (35.8)	-	55 (37.4)	0.736
Cod-liver oil	-	*36 (26.9)*	-	*36 (24.5)*	0.458
ώ-3 capsules	-	*49 (36.6)*	-	*43 (29.3)*	0.117
Multivitamins	-	*25 (18.7)*	-	*20 (13.6)*	0.327
Other	-	*22 (16.4)*	-	*28 (19.0)*	0.839

The table continues on the next page.

Table 12c.Comparisons of dietary results from Smart Diet at V1 and V3

Number of attending subjects		V1 n=156		V3 n=156	P-value V1-V3
	n[a]		n[a]		
SmD-score, p[§]	123	35.5 (34.8, 36.1)	123	36.3 (35.7, 36.9)	0.010*
SmD-catecory[‡]	139	89.1	153	98.1	0.020*
1 (<30 p)	-	9 (6.5)	-	4 (2.6)	-
2 (30-37 p)	-	88 (63.3)	-	86 (56.2)	-
3 (≥38 p)	-	42 (30.2)	-	63 (41.2)	-
SmD-subgroups					
Dairy (4-12 p)[§]	126	10.2 (9.9, 10.4)	126	10.0 (9.8, 10.2)	0.263
Meat (3-6 p)[¶]	126	6.0 (5.0-6.0)	126	6.0 (5.9-6.0)	0.030*
Fish (3-6 p)[§]	125	3.9 (3.6, 4.1)	125	4.0 (3.8, 4.2)	0.171
Fruit and vegetables (1-3 p)[§]	126	2.1 (2.0, 2.2)	126	2.2 (2.1, 2.3)	0.058
1 (<2 portions/day)[‡]	-	*20 (15.9)*	-	*11 (8.7)*	-
2 (2-4 portions/day)[‡]	-	*73 (57.9)*	-	*75 (59.5)*	-
3 (>4 portions/day)[‡]	-	*33 (26.2)*	-	*40 (31.7)*	-
Vegetables (1-3 p)[§]	117	1.7 (1.6, 1.9)	117	1.9 (1.8, 2.1)	0.011*
1 (<1 portions/day)[‡]	-	*50 (42.7)*	-	*33 (28.2)*	-
2 (1-2 portions/day)[‡]	-	*47 (40.3)*	-	*60 (51.3)*	-
3 (≥3 portions/day)[‡]	-	*20 (17.1)*	-	*24 (20.5)*	-
Fruit (1-3 p)[§]	117	2.0 (1.9, 2.1)	117	1.9 (1.8, 2.1)	0.296
1 (<1 portions/day)[‡]	-	*34 (29.1)*	-	*40 (34.2)*	-
2 (1-2 portions/day)[‡]	-	*51 (43.6)*	-	*48 (41.1)*	-
3 (≥3 portions/day)[‡]	-	*32 (27.4)*	-	*29 (24.8)*	-
Dietary supplements[‡]	129	82.7	147	94.2	-
None	-	41 (31.8)	-	55 (37.4)	0.362
Cod-liver oil	-	*35 (27.1)*	-	*36 (24.5)*	0.728
ώ-3 capsules	-	*58 (45.0)*	-	*43 (29.3)*	0.016*
Multivitamins	-	*24 (18.6)*	-	*20 (13.6)*	0.248
Other	-	*19 (14.7)*	-	*28 (19.0)*	0.541

Data are given as mean [§](95% CI), [¶]median (25-75 percentiles) or [‡]number (%).
[a]Indicates total number of measured subjects.
V1 *visit 1,* V2 *visit 2,* V3 *visit 3,* SD *Smart Diet,* p *points,* CI *confidence interval*.
For calculation of p-values [§]paired t-test, [¶]Wilcoxon signed rank test or [‡]McNemar Bowker Test was used.
*Significant change at p<0.05

Lifestyle factors

Table 13a, 13b and **13c** present lifestyle results from SmD. During the study period, the proportion that was smokers showed a small decrease from approximately 18% to 14% (non-significant). The proportion of those who consumed alcohol was also relatively stable during the study period, and no significant changes were observed. The proportion with a moderate consumption of alcohol (one to seven units a week) was stable with a proportion of approximately 50%. Regarding physical activity, there were no significant differences in the amount reported at the three visits.

Table 13a. Comparisons of lifestyle results from Smart Diet at V1 and V2.

Number of attending subjects	V1 n=156		V2 n=147		P-value V1-V2
	n[a]	n (%)	n[a]	n (%)	
Smoking	123		123		0.894
No		100 (81.3)		101 (82.1)	
Yes, number of cigarettes		23 (18.7)		22 (17.9)	
≤5		6 (4.9)		4 (3.3)	
6-10		6 (4.9)		7 (5.7)	
≥11		5 (4.1)		3 (2.4)	
Party smoker		6 (4.9)		8 (6.5)	
Alcohol consumption[b]	112		112		0.106
0		18 (16.1)		16 (14.3)	
<1		31 (27.7)		27 (24.1)	
1-7		55 (49.1)		58 (51.8)	
8-14		6 (5.4)		11 (9.8)	
≥15		2 (1.8)		0 (0.0)	
Physical activity[c]	118		118		0.566
Never		1 (0.8)		1 (0.8)	
<1		16 (13.6)		17 (14.4)	
1-2		51 (43.2)		44 (37.3)	
≥3		50 (42.4)		56 (47.5)	

Table 13b. Comparisons of lifestyle results from Smart Diet at V2 and V3.

Number of attending subjects	V2 n=147		V3 n=156		P-value V2-V3
	n[a]	n (%)	n[a]	n (%)	
Smoking	132		132		0.303
No		109 (82.6)		114 (86.4)	
Yes, number of cigarettes		23 (17.4)		18 (13.6)	
≤5		5 (3.8)		2 (1.5)	
6-10		7 (5.3)		4 (3.0)	
≥11		3 (2.3)		8 (6.0)	
Party smoker		8 (6.1)		4 (3.0)	
Alcohol consumption[b]	127		127		0.064
0		18 (14.2)		17 (13.4)	
<1		30 (23.6)		39 (30.7)	
1-7		65 (51.2)		62 (48.8)	
8-14		14 (11.0)		9 (7.1)	
≥15		0 (0.0)		0 (0.0)	
Physical activity[c]	129		129		0.747
Never		1 (0.8)		3 (2.3)	
<1		17 (13.2)		17 (13.2)	
1-2		47 (36.4)		38 (29.5)	
≥3		64 (49.6)		71 (55.0)	

The table continues on the next page.

Table 13c. Comparisons of lifestyle results from Smart Diet at V1 and V3.

Number of attending subjects	V1 n=156		V3 n=156		P-value V1-V3
	n[a]	n (%)	n[a]	n (%)	
Smoking	142		142		0.584
No		116 (81.7)		122 (85.9)	
Yes, number of cigarettes		23 (16.2)		20 (14.1)	
≤5		7 (4.9)		2 (1.4)	
6-10		6 (4.2)		4 (2.8)	
≥11		6 (4.2)		10 (7.0)	
Party smoker		7 (4.9)		4 (2.8)	
Alcohol consumption[b]	131		131		0.772
0		20 (15.3)		19 (14.5)	
≤1		39 (29.8)		41 (31.3)	
1-7		62 (47.3)		62 (47.3)	
8-14		8 (6.1)		9 (6.9)	
≥15		2 (1.5)		0 (0.0)	
Physical activity[c]	137		137		0.443
Never		2 (1.5)		4 (2.9)	
≤1		20 (14.6)		20 (14.6)	
1-2		59 (43.1)		44 (32.1)	
≥3		56 (40.9)		69 (50.4)	

Data are given as number (%).

[a]Indicates total number of measured subjects.

[b]Categorized as number of units consumed weekly. One unit is defined as 125 mL wine, 330 mL beer or 4 cL spirits.

[c]Categorized as number of sessions > 30 minutes weekly.

V1 *visit 1*, V2 *visit 2*, V3 *visit 3*

For calculation of p-values Wilcoxon Signed Rank test was used.

*Significant change at $p<0.05$

4.2.4 **Patients preferences concerning the treatment**

The patient's preference form was only collected at V1 and V3. Only the question about the acceptance of having adverse effects to achieve a low cholesterol level showed a significant change during the study period. These results are shown in **table 15.**

Table 14. Comparisons of the patient's preference form at V1 and V3

Number of attending subjects	V1 n=156		V3 n=156		P-value
	n[a]	n (%)	n[a]	n (%)	
A healthy lifestyle is as important as medicines	119		119		0.163
Fully agrees		71 (59.7)		74 (62.2)	-
Partly agrees		33 (27.7)		37 (31.1)	-
Neither nor		6 (4.8)		2 (1.7)	-
Partly disagrees		7 (4.6)		5 (4.2)	-
Fully disagrees		2 (1.6)		1 (0.8)	-
I prefer to have as low cholesterol as possible	119		119		0.269
Fully agrees		93 (78.2)		85 (71.4)	-
Partly agrees		21 (17.6)		28 (23.5)	-
Neither nor		3 (2.5)		3 (2.5)	-
Partly disagrees		2 (1.7)		1 (0.8)	-
Fully disagrees		0 (0.0)		2 (1.7)	-
A low cholesterol is more important than not having adverse effects[b]	120		120		0.001*
Fully agrees		10 (8.3)		13 (10.8)	-
Partly agrees		14 (11.7)		27 (22.5)	-
Neither nor		22 (18.3)		31 (25.8)	-
Partly disagrees		41 (34.2)		34 (28.3)	-
Fully disagrees		33 (27.5)		15 (12.5)	-

Data are given as number (%).

[a]Indicates total number of measured subjects.

[b]Original statement: I prefer to have little adverse effects rather than low cholesterol.

V1 *visit 1*, V3 *visit 3*.

For calculation of p-values Wilcoxon signed ranks test was used.

*Significant change at $p<0.05$

4.3 Comparisons of patients with and without CVD at V3

4.3.1 Clinical characterization

The number of patients with CVD increased significantly from 34 patients (21.8%) at V1 to 49 patients (31.4%) at V3 at $p<0.001$ (data not shown). The age at V3 was very different; those with CVD were on average 11.6 years older than those who had not experienced any CV. Importantly they were also diagnosed with FH on average approximately 13 years later. More males than females had CVD (**table 15**).

The youngest patient had first CVD event at age 25.2 years of age (data not shown). As shown in **table 16** and **15** respectively, mean age at first CV event and age at FH-diagnosis among patients with CVD were about the same. Table 16 also shows an overview over type of CV events the patients had experienced.

Men with CVD had a significant higher WC than men without CVD. Both men and women with CVD had a higher median BMI compared to men and women without CVD; however the difference was not significant (table 16).

4.3.2 **CVD among deceased patients**

Of the 357 patients included at V1, 12 patients (3.4%) died during study period (data not shown). The median age at time of death was 64.3 years (25-75p: 47.3-67.5 years). We had no access to the death certificates; however we had access to their medical journals. After reviewing their medical journals, we can with certainty say that 3 of these (25.0%) died because of CVD; one of acute coronary syndrome, one of heart failure and one of AMI. Causes of death are unknown for four patients (33.3%), however two of them had CVD and one of them had besides a kidney transplant. Of the two remaining patients, one was a drug abuser and one had an inadequate journal, but this patient was free from CVD in 2007. Three patients (25.0%) suffered from cancer by the time of their death; in addition one of them had suffered from CVD. The two remaining patients were free from CVD by the time of their death. One went into multi organ and respiratory failure and one died in a traffic accident. Taken together, at least six of the deceased patients (50.0%) had established CVD.

4.3.3 **Blood parameters**

As seen in table 16, patients with CVD had a higher untreated cholesterol levels than the patients without CVD. At V3, however, there were no significant differences in TC and LDL-C between the two groups.

Patients with CVD had a more metabolic blood profile compared to patients free from CVD, with higher levels of TG, fasting glucose and HbA1c. HDL-C also tended to be lower among patients with CVD, but the difference was not significant (table 16). **Figure 4** illustrates the difference in the metabolic parameters between the two groups.

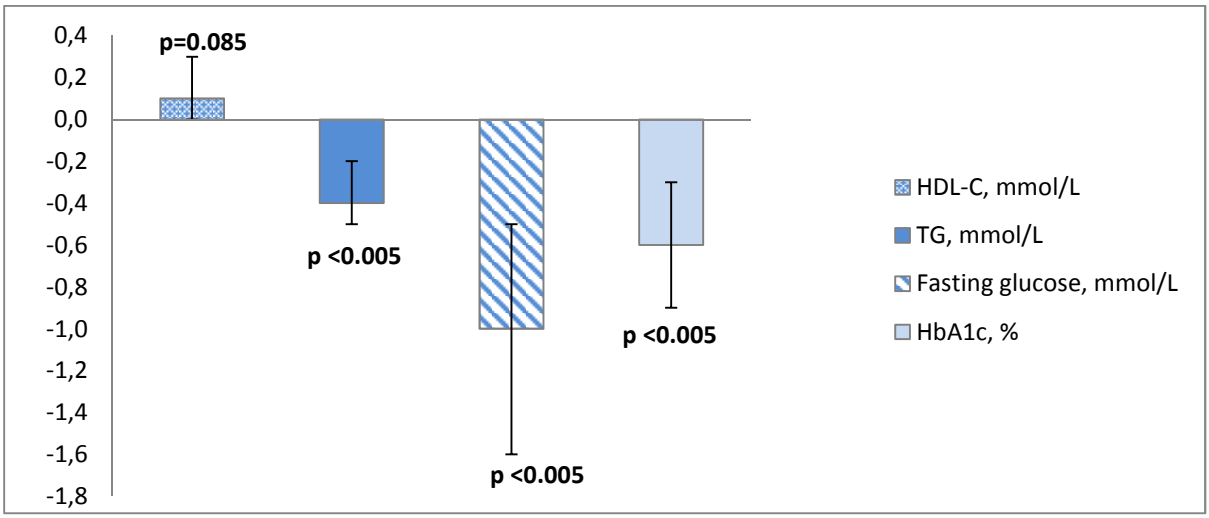

Figure 4. Difference in metabolic blood parameters between patients with and without CVD at V3.

Data are given as mean (95% CI).

V3 *visit 3*, CI *Confidence interval*, TC *total cholesterol*, HDL-C *High-density lipoprotein cholesterol*, TG *triglycerides*.

4.3.4 **Metabolic comorbidities**

An overview over the proportion with metabolic comorbidities is shown in table 16. There were a higher proportion of patients with abdominal obesity in the CVD-group; however, the difference in WC was only significant among men. In addition, patients with CVD disease had a significant higher prevalence of metabolic syndrome, based on both the criteria of NCEP ATP III and IDF.

4.3.5 **Medication**

Lipid lowering medication is shown in table 16. Patients with CVD were mostly treated with high intensity statin therapy and with three or more LLMs. 69.4% of the patients with CVD were treated with antihypertensive medication. This was a significantly higher proportion ($p<0.005$) than the 11.2% in the non-CVD group (data not shown). No difference in the proportion treated with glucose lowering medication was found (data not shown).

Table 15. Comparisons of characterization of patients with CVD and without CVD at V3.

	CVD n=49		No CVD n=107		P-value
Clinical characteristics	**n[a]**		**n[a]**		
Age at V3, *years*[§]	49	60.9 (58.4, 63.5)	107	49.3 (46.8, 51.7)	<0.005*
Age at FH-diagnosis, *year*[§]	49	42.7 (39.4, 45.9)	102	29.8 (26.8, 32.7)	<0.005*
Waist, *cm*[§]					
Male	27	104.8 (98.8, 110.9)	47	98.0 (94.0, 100.5)	0.016*
Female	15	92.8 (85.4, 100.2)	51	90.3 (86.2, 94.4)	0.548
BMI, kg/m^2 [§]					
Male	31	29.0 (26.7, 31.2)	49	27.0 (25.8, 28.1)	0.112
Female	18	27.5 (25.4, 29.6)	58	26.6 (25.0, 28.2)	0.480
Sex[ǂ]	49		107		
Male		31 (63.3)		49 (45.8)	0.043*
Female		18 (36.7)		58 (54.2)	0.043*
Fasting blood parameters	**n[a]**		**n[a]**		
Untreated TC, *mmol/L*[§]	45	10.9 (10.1, 11.6)	104	9.3 (9.0, 9.7)	<0.005*
Untreated LDL-C, *mmol/L*[§]	36	7.1 (6.2, 8.0)	76	7.0 (6.6, 7.4)	0.838
TC, *mmol/L*[§]	49	5.0 (4.7, 5.4)	107	5.2 (4.9, 5.5)	0.539
HDL-C, *mmol/L*[§]	49	1.3 (1.2, 1.5)	107	1.5 (1.4, 1.6)	0.085
LDL-C, *mmol/L*[§]	49	3.1 (2.8, 3.4)	107	3.2 (2.9, 3.5)	0.539
TG, *mmol/L*[§]	49	1.4 (1.2, 1.7)	106	1.0 (1.0, 1.1)	<0.005
Fasting glucose, *mmol/L*[§]	48	6.4 (5.8, 7.0)	105	5.4 (5.1, 5.6)	<0.005
HbA1c, *%*[§]	45	6.2 (5.9, 6.5)	95	5.6 (4.5, 5.7)	<0.005
Comorbidities	**n[a]**		**n[a]**		
Abdominal obesity[c][ǂ]					
Men	27	14 (51.9)	47	12 (25.5)	0.022*
Women	15	10 (66.7)	51	25 (49.0)	0.229
Metabolic syndrome, defined by					
NCEP ATP III[ǂ]	48	26 (54.2)	107	18 (16.8)	<0.005*
IDF[ǂ]	44	23 (52.3)	107	24 (22.4)	<0.005*
Lipid lowering medication[d]	**n[a]**		**n[a]**		
No statin therapy[ǂ]	49	3 (6.1)	107	10 (9.3)	0.231
High intensity statin therapy[ǂ]	49	44 (89.8)	107	76 (71.0)	0.010*
Moderate intensity statin therapy[ǂ]	49	3 (6.1)	107	20 (18.7)	0.034*
PCSK9-inhibitors[ǂ]	49	0 (0.0)	107	2 (1.9)	0.335
≥2 lipid lowering medications[ǂ]	49	42 (85.7)	107	78 (72.9)	0.119
≥3 lipid lowering medications[ǂ]	49	24 (49.0)	107	18 (16.8)	<0.005*

Data are given as mean [§](95% CI) [¶]median (25-75 percentiles) or [ǂ]number (%).

[a]Indicates total number of measured subjects.

[b]Abdominal obesity is defined as a waist circumference >102 cm for men and >88 cm for women.

[c]≥2 lipid lowering medications: least a statin and ezetimbe,≥3 lipid lowering medications: least a statin, ezetimibe and colesevelam. High intensity statin therapy: atorvastatin 40-80 mg or rosuvastatin 20-40 mg. Moderate intensity statin therapy: atorvastatin 10-20 mg, rosuvastatin 5-10 mg, pravastatin 40-80 mg, simvastatin 20-40 mg, lovastatin 40 mg, fluvastatin 40 mg or pitvastatin 2-4 mg.

CVD *cardiovascular disease* V3 *visit 3,* CI Confidence interval, TC *total cholesterol,* LDL-C *Low-density lipoprotein cholesterol*, HDL-C *High-density lipoprotein cholesterol*, TG *triglycerides,* PCSK9 *proprotein subtilisin/kexin type 9,* NCEP ATP III *National Cholesterol Education Program Adult Treatment Panel III, IDF International Diabetes Federation,* OUS *Oslo University Hospital*.

P-value calculated with [§]independent t-test, [¶]Mann-Whitney U Test, [ǂ] Chi-square test.

Pairwise exclusion was used for handling of missing values.

*Significant change at p<0.05

Table 16. Cardiovascular events

Number of patients with CVD at V3, n=49	
Age at first CV event, years[§]	45.7 (42.6, 48.3)
Number of MI's[‡]	20 (40.8)
Number of PCI's[‡]	22 (44.9)
Number of AP[‡]	30 (61.2)
Number of carotid stenosis[‡]	12 (24.5)
CABG[‡]	18 (36.7)
Aortic aneurysm[‡]	6 (12.2)
Cerebrovascular event[a]	10 (20.4)

Data are given as mean [§](95% CI) or [‡]number(%).

[a]Includes transient ischemic attack, ischemic stroke and haemorrhagic stroke

CI *Confidence interval*, CVD *cardiovascular disease*, CV *cardiovascular*, MI's *Myocardial infarctions*, PCI's *Percutaneous coronary interventions*, AP *Angina pectoris*

4.3.6 **Diet and lifestyle**

SmD-results are presented in **table 17.** Patients with CVD reported to eat more fish than the patients without CVD, while patients without CVD reported to eat more vegetables. There were no differences in amount of physical activity, alcohol consumption, proportion of current smokers, or in the number taking dietary supplements (data on dietary supplements are not shown). Among the patients with CVD there was a significant higher proportion with former smokers. Half of the patients with CVD reported to be former smokers, compared to one third among the patients CVD.

Table 17. Diet and lifestyle characterization of patients with CVD vs. no CVD at V3

	CVD n=49		No CVD n=107		P-value
Diet	**n[a]**		**n[a]**		
SmD-score, p[§]	40	36.9 (35.9, 37.8)	100	36.3 (35.6, 37.0)	0.361
SmD-category[ǂ]	49	2.3 (2.2, 2.5)	104	2.5 (2.3, 2.6)	0.208[‡]
1 (<28 p)	1	1 (2.1)	3	3 (2.8)	
2 (29-37 p)	23	23 (48.9)	63	63 (59.4)	
3 (>38 p)	23	23 (48.9)	40	40 (37.7)	
SmD-subgroups					
Dairy, (4-12 p)[§]	47	10.3 (9.9, 10.7)	106	9.9 (9.7, 10.2)	0.134
Meat, (3-6 p)[¶]	47	6.0 (6.0-6.0)	106	6.0 (6.0-6.0)	0.708
Fish, (3-6 p)[§]	47	4.4 (4.1, 4.7)	106	3.8 (3.6, 4.1)	0.007*
Fruit and vegetables, (1-3 p)[§]	47	2.1 (1.9, 2.3)	106	2.3 (2.1, 2.4)	0.356[‡]
1 (<2 portions/day)[ǂ]		7 (14.9)		7 (6.6)	
2 (2-4 portions/day)[ǂ]		26 (55.3)		66 (62.3)	
3 (>4 portions/day)[ǂ]		14 (29.8)		33 (31.1)	
Fruit, (1-3 p)[§]	41	2.0 (1.9, 2.3)	100	1.9 (1.8, 2.2)	0.957[‡]
1 (<1 portions/day)[ǂ]		15 (36.6)		32 (32.0)	
2 (1-2 portions/day)[ǂ]		15 (36.6)		45 (45.0)	
3 (≥3 portions/day)[ǂ]		11 (26.8)		23 (23.0)	
Vegetables, (1-3 p)[§]	41	1.7 (1.5, 2.0)	100	2.0 (1.9, 2.1)	0.020[‡]*
1 (<1 portions/day)[ǂ]		18 (43.9)		25 (25.0)	
2 (1-2 portions/day)[ǂ]		18 (43.9)		51 (51.0)	
3 (≥3 portions/day)[ǂ]		5 (12.2)		24 (24.0)	
Lifestyle	**n[a]**		**n[a]**		
Physical activity[b,ǂ]	49		107		0.523[‡]
Never		2 (4.1)		3 (2.8)	
<1		9 (18.4)		13 (12.1)	
1-2		13 (26.5)		36 (33.6)	
≥3		25 (51.0)		55 (51.4)	
Alcohol intake[c,ǂ]	49		106		0.236[‡]
Never		11 (22.4)		12 (11.3)	
<1		13 (26.5)		32 (30.2)	
1-7		21 (42.9)		55 (51.9)	
≥8		4 (8.2)		7 (6.6)	
Current smokers[ǂ,d]	49	7 (14.3)	106	15 (14.0)	0.986
Former smokers[ǂ]	49	25 (51.0)	107	36 (33.6)	0.039*

Data are given as mean [§](95% CI) [¶]median (25-75 percentiles) or [ǂ]number (%).

[a]Indicates total number of measured subjects.

[b]Categorized as number of sessions > 30 minutes weekly.

[c]Categorized as number of units consumed weekly. One unit is defined as 125 mL wine, 330 mL beer or 4 cL spirits.

V3 *visit 3,* CI *Confidence interval,* SmD *Smart Diet,* p *points*.

P-value calculated with an [§]independent t-test, an [¶]Mann-Whitney U Test, a [ǂ]Chi-square test.

[‡]P-value indicates p for trend

Pairwise exclusion was used for handling of missing values.

*Significant change at p<0.05

5 Discussion

In the present study long-term aggressive lipid lowering treatment of FH-patients in an outpatient Lipid clinic resulted in lower TC and LDL-C after eight to ten years. On the other hand, fasting glucose, HbA1c, TG, weight, BMI and WC increased. Another important finding was that FH-patients with CVD were older and had higher levels of fasting glucose, HbA1c, TG, pre-treatment TC and occurrence of MetS than those without CVD. Further, patients with CVD were diagnosed with FH later in life compared to patients without CVD.

5.1 Subjects and methods

This thesis is a continuation of the thesis by Marlene Thorvall (148), where additional FH-patients was included to get a better basis for generating hypothesis and drawing conclusions.

5.1.1 Participants

As the general population, patients with FH are a heterogeneous group consisting of more or less motivated and compliant patients. Many FH-patients has experienced CVD themselves or in close family, thus many are fully aware of the increased CV risk FH causes. Hence, they are well prepared to see the importance of adequate treatment, and thus should be motivated and compliant. However, the improved treatment leads to fewer patients experiencing the serious consequences of FH, such as sudden or early death. Less knowledge about the potential risk FH entails may lead to lower motivation and compliance towards the treatment.

The study population may be affected by selection bias towards motivated and compliant participants, although most of those who were asked to participate agreed initially. At V3 50% of those who attended V1 were no longer registered as patients at the Lipid Clinic and their FH was handled by other health care providers than the Lipid Clinic. Patients who do not wish further follow-up or do not meet for the consultations repeatedly, lose their position in the waiting list, and need a new referral from their GP to get a new consultation. This could be a selected group of non-motivated and non-adherent patients. Often, patients who participate in long-term studies are more educated, and may be healthier than the general population (156, 157). On the other hand, patients who no longer receive follow-up at the Lipid Clinic might not be the same patients who do not attend long-term studies. They might

get sufficient follow-up with their GP, or receive follow-up for their FH at another specialized outpatient clinic in Norway. Whether the former patients are more or less motivated and adherent, anywise if they differ from our study population, the internal and external validity of our results are affected. During the spring 2017, V3 part III will be implemented and aims to reach these patients. Thus, it would be of interest to investigate if inclusion of these patients alters the findings from this thesis.

At the very first-time consultation at the Lipid Clinic, prior to V1 in the present study, patients receive dietary counselling with a clinical dietician. Further, patients with FH are offered regular consultations (annually to every third year) with doctors, and additionally consultations with clinical dieticians if necessary and they were therefore very well informed about lipid lowering diet prior to V1 reducing the potential for further improvement during the study period. At each consultation the patient's diet and lifestyle is assessed by SmD, which might contribute to an increased awareness of their diet and lifestyle. Further, they are well aware of the treatment provider's anticipations and recommendations regarding the treatment. This can intentionally or unintentionally, cause pleasing bias. Our data on diet and lifestyle are most susceptible. In this setting the patient knows what is healthy to eat and what the clinical dietician/doctor recommends. The patient answers in a way that fulfils this, though it does not necessarily correspond to the patient's actual dietary habits. To minimize pleasing bias, the patients filled out SmD at the waiting room prior to each consultation as pleasing bias also can occur during the consultation with the clinical dietician/master student.

Some patients were off LLM of various reasons at V3. As the study initially was a quality assessment of the treatment given at the Lipid Clinic, one of the exclusions criteria was being off LLM at the study start. Thus patients who were off LLM at V1 were excluded, and were not invited to further participate in the subsequent visits. However, at V3 we included the patients who were off LLM at the present time, as they are a normal variation within the treatment state.

5.1.2 **Study design and implementation of the study**

The TTT-FH is a prospective study, where the collected data describes the state at the time of the visits. Only pre-treatment cholesterol levels and CV events was collected retrospectively. Collection of data about diet, lifestyle and preferences towards the treatment in a prospective manner minimizes the potential for recall bias. However, as some of the patients had CVD

before V1 and during the study period, we cannot rule out that this affected their registration in some way. The comparisons of patients with and without CVD have a cross-sectional design, as all variables with exception of pre-treatment TC and LDL-C was collected at V3. As we are unable to claim any about the order of the exposure factor and the CVD, no causality is provided. However, our findings could be interpreted as of areas for future research.

If data is collected differently for different patients, it can lead to information bias. This is mostly applicable to the data collected by the doctor during the consultations. Everyone who has collected data in the study has worked by the same protocol. Generally, each patient met the same doctor at V1 and V2. At V3, all patients met the same doctor, with some minor exceptions. The doctor who conducted V3 was the same doctor who met most of the patients on V1 and V2 (43.4% and 46.1%, respectively) thereby reducing the variation in the collection of information within each patient. On V1 and V2 some of the patients had additional consultations with a clinical dietician, which generally leads to an adjustment in the SmD. Therefor some of the SmD-results from V1 and V2 are adjusted, while others are unadjusted. However, the adjustment can be in both directions, thus it is likely to assume that this had a neutral effect on the SmD-results.

It is difficult to collect reliable data on diet, as the methods for data collection are affected with different bias (158, 159). SmD was developed for utilization in clinical settings. It is validated, and provides a good estimate of the intake of fat and fibre, but is less accurate in the terms of vegetables, fish and snacks. It gives an opportunity to discuss central points in the patients dietary habits and is a useful health education tool, thus it has a high value in a clinical setting (153). The value of SmD in research purposes is uncertain. However, as this study takes place in an outpatient clinic and initially aimed to evaluate the effect of the treatment, it was natural that SmD was used in the dietary assessment. We used different SmD-versions in this study. Due to too large divergence from the total scoring in the 2003-version, total score from the 2007- and 2009-version was not registered, leading to several missing values. Category and point score for each of the food categories in the different versions were registered, as it did not affect the results in any direction.

Weight and height was collected with the same devices, while BP was collected with two calibrated devices at V3. The measurements was standardized and mostly collected by the same persons. However, some deviations from this could have weakened our results. During

the visits, weight was measured at different time during the day. Thus, eating and toilet visits might have influenced the weight. We assume that this affected our results in both ways, and thus yielded a neutral effect. At V1 and V2 there is a chance that some of the heights are self-reported. Self-reported heights can be inaccurate since many cannot remember their accurate height (150). Height gradually decreases from 30 years of age; however the reduction is not of a particular size until after the age of 50 or 60 years of age in women and men, respectively (160). We chose to calculate BMI by using height measured on V3, thus we might have underestimated the increase in BMI. Nevertheless, we assume that using self-reported height at V1 and V2 would have biased the results to a bigger extent.

Smokers were classified as those who smoked on a regular basis and those who smoked occasionally, preferably at parties. This might have biased our results as the amount of party smoking depends on how often the patient's parties. However, analysis with and without party smokers classified as regular smokers did not alter the results.

Age at FH-diagnosis was calculated from the date when the patients had their first-time consultation at the Lipid Clinic (usually prior to the date for genetic diagnosis), meaning that this date corresponds to when they got their clinical diagnosis. This is probably a minor underestimation of the age at diagnosis as other doctors might have clinically diagnosed some patients at a previous time.

We do not have a control group; therefor it is possible that our results might have been influenced of other factors than the treatment given at the Lipid Clinic. On the other hand, in this setting choosing the right control group is difficult. Of ethical reasons, we cannot refrain from offering treatment to FH-patients. Moreover, using healthy subjects provides a wrong comparisons basis. An outpatient setting with less controlled circumstances compared to controlled clinical trials can be positive, as it increases the generalizability to the general treatment given to FH-patients. In a controlled clinical trial the contact with health professionals are more frequent than in an outpatient setting, thus the generalizability could be impaired. Therefore, we believe that the results from our study may be indicative of what is achievable with aggressive lipid lowering treatment in compliant and motivated FH-patients.

Initially, we collected data on Lp(a) for all patients, however due to changes in the assay methods over the years and missing information on when Lp(a) was analysed in our population, we could not use an adjustment factor to obtain comparable Lp(a) data. Today,

Lp(a) assay methods measures the number of molecules in nmol/L, where levels above 75 nmol/L indicates an increased risk for CVD. In the 2000s, the assay methods measured the mass, which does not correspond well with the number of particles. During the 1990s and 2000s the 75th percentile in the general population has changed according to changes in the assay methods. It has been both 450 mg/L and 300 mg/L (2016, Helge Rootwelt, personal communication). Missing information about Lp(a) levels in this FH-population is an limitation, since other studies has found Lp(a) to be higher among FH-patients compared to the general population (161, 162) and higher among FH-patients with CVD compared to patients without CVD (163).

5.1.3 **Data processing**

In the data from the two earliest visits there are several values missing, especially regarding anthropometric data, BP, intensity of physical activity and SmD. These missing values are classified as item non-response. To avoid missing information we used pairwise exclusions in the analysis where it was necessary. A high content of missing values can potentially bias our results if they originate from a selected group of patients. However, we assume that the missing values are a result of random sloppiness by the doctors; they have forgotten to measure and/or document weight, WC and BP in the journal. The missing values in the SmD results partly from the use of three different SmD-variants in the study, partly from patients forgetting to tick off for some questions and to finish the SmD prior to the consultations. Again, sloppiness by the doctors appears. Some doctors are too lousy to review SmD thorough enough to notice and comment on small errors. This demonstrates the importance of having separate consultations with clinical dieticians in order to obtain reliable and precise data on diet and lifestyle. Nevertheless, a high proportion of missing values weaken our study strength. The weakness of having missing values became apparent when performing paired analytical tests on variables measured at different time points. These tests require present values for each individual at each time point. Presence of many missing values reduces the number and the statistical power to detect differences and generalize the findings. However, we performed analytical and descriptive analyses of all visits and V3 alone, respectively. No major differences in measures of central tendency at V3 calculated in the descriptive analyses or in the analytical were detected, except for WC, suggesting that over findings in the analytical analyses are representative for our population.

When exploring a large number of differences there is an increased risk of type 1 error. To control for this error we could use Bonferroni adjustment, however due to this thesis being explorative and descriptive, we decided not to adjust. With Bonferroni adjustment a p-value <0.0016 would be considered significant. Thus, caution should be made since we might wrongly accept or rejected some differences on an insufficient basis, but our highly significant findings would not disappear with Bonferroni adjustment.

As described in the section 3.3, our data was quality controlled to minimize accidental bias from the plotting process. The master students plotted all variables. As they were in accordance to each other, inter-variability, both differential and non-differential, between the variables was avoided to the greatest extent.

5.2 Results

5.2.1 Present state at V3 and changes during eight to ten years

FH-diagnosis

In this study we had a very high proportion of patients with a genetic verified FH-diagnosis. This is considered a strength as we have excluded most patients with a phenotypic FH, where a polygenic basis is responsible for the elevated LDL-C (9). As far as we know, no other similar studies evaluating the treatment effect in FH-patients has such a high percentage of genetic verified FH-patients (164, 165). It should be pointed out that the genetic testing performed in Norway has a high sensitivity and specificity, higher than in most other countries (166).

Unfortunately, the patients mainly got their clinical diagnosis in their adulthood. Undiscovered and untreated FH increases the cholesterol burden and leads to an earlier threshold for CVD compared to optimal treated FH-patients (9). The importance of an early diagnosis is important in many aspects. First, initiation of lipid lowering treatment is critical to reduce the cumulative cholesterol burden and the excess CV risk (9). Second, dietary habits are acquired early in life (167, 168). Consequently, a cardioprotective diet and dietary counselling ideally starts in childhood (169). Molven et al found that FH-children who had received dietary counselling had healthier food-choices than non-FH-children. This was also the case with FH-adolescents, indicating that dietary habits achieved in childhood lasts into

early adulthood (170). Probably, this applies to other healthy habits, as being a non-smoker and physical active.

To identify new FH-subjects cascade screening is recommended, as it is the most cost-effective approach (9, 171). Initially, GP needs to measure cholesterol levels among their patients, including younger patients. If deviating values are present, genetic testing is necessary to ensure a definite diagnosis. If the genetic test is positive, remaining family members should be tested. Child-parent screening has also been proposed as a simple, practical and effective way of screening to identify and prevent premature CVD (172).

Medications

The intensity of the LLM is decided based on mainly four factors; the need for LDL-C reduction, the presence of other CV risk factors, the patient's perceived adverse effects and their attitudes towards the medical treatment. Clearly, three quarters of the patients needed and were treated with a high intensity statin, and the same amount needed and was treated with Ezetimibe as an adjunctive medication. Further, nearly 30% needed additional lipid lowering treatment with colesevelam.

As FH does not lead to elevated TGs, presence of elevated TG is a result of other factors, typically an unhealthy diet and lifestyle (173). The finding of that only three patients used high dose omega-3, could be interpreted as a consequence of new studies suggesting that omega-3 has limited effects on CV risk (174-176).

Two patients used PCSK9-inhbitors. From 15th of December 2015, applications for treatment with PCSK9-inhibitors were submitted for 27 patients. On average the patients had BP within the normal range; however a third of the patients were treated with antihypertensive medications, indicating that elevated BP was a problem for these patients.

The prevalence of DM was three times higher than the estimated prevalence of approximately 4% in the general Norwegian population (177). In a study of 79 deceased FH-patients in Norway, the rate of DM was 22%, suggesting that DM represents a major risk factor for death in FH patients (12). As the rate of DM in a deceased population is not representative for the general FH-population, the DM-rate in our study may be of relevance for the incidence of DM in FH. However, since we based our prevalence on those who use glucose lowering medication, the actual prevalence might be higher as some patients might have undiagnosed

DMT2 or being treated with only diet and exercise (178, 179). Future studies in the TTT-FH study should investigate the incidence of DM more closely.

We can assume that the vast majority of the patients started statin therapy immediately after their first-time consultation at the Lipid Clinic, but there might be a few exceptions. Some of the patients might have been treated with statins prior to the first-time consultation, while others might started statin therapy a while after due to too young age or FH-diagnosis in the pre-statin-era. Further, some of the patients had periods where they were not treated with statins, for example during pregnancy and breast-feeding. However, we assume that the patients on average have been treated with statins for at around 19 years. This is a much longer time period than in the follow-up in studies showing a diabetogenic effect of statins, which in general had follow-up time of four to five years (113, 180). In a meta-analysis of 13 statin trials with a mean duration of four years, statin therapy was associated with a 9% increased risk for incident DM. Compared with moderate statin therapy, intensive statin therapy increases the risk (181). The finding of a higher presence of DM in addition to the increase in HbA1c and fasting glucose among patients with long-term statin therapy might indicate that these findings can be attributable to the statin therapy.

Adverse effects

The occurrence of adverse effects from current statin therapy in the present study was in accordance with a similar Dutch study where 27.4% had adverse effects from current statin therapy (182) . However, these rates are higher than the rates of adverse effects found in RCTs. Saxon et al, proposes that the exclusion of certain patients from RCTs such as elderly, patients with comorbidities, and those with prior history of or current muscle-related symptoms leads to these results (183). In RCTs standard dose statin treatment typically confers an excess risk of myopathy of 0.01% (184, 185). This percentage derives from subtracting the rate of adverse effects in placebo from active medication. The Heart Protection Study found an occurrence of muscle pain of approximately 30% in both the simvastatin and placebo group (185). Without a control group it is difficult to assess adverse effects caused by the medical treatment.

Compared to observational studies muscular symptoms was more common in our study. In another study, 10% reported having muscular symptoms due to statin therapy, which is less than half of what we observed (186). Furthermore, comparing rates of adverse effects in

different studies can cause problems, as the rates depend on how adverse effects are measured. Use of questionnaires allows for a subjective assessment of the presence of adverse effects, while assessment by a doctor gives an objective evaluation and might affect the results. As we only assessed adverse effects from current used medication, it is probable that the prevalence of those experiencing adverse effects would have been even higher if we assessed both current and former medication.

Patients with no statin therapy at V3

It is interesting to increase the knowledge about why some FH-patients choose not to be treated with statins, and accepts the elevated cholesterol levels and being at high CV risk. Benn et al found that non-statin treated FH-patients had a 13-fold increased CVD risk compared to statin treated FH-patients (187). Adherence rates to prescribed drug regimens are low among patients with chronic diseases (188, 189). The World Health Organization reports that adherence among patients suffering from chronic disease is on average 50%. In our population 8.3% were off statin therapy, however, this in an underestimation of the adherence rate as general adherence towards medical regimes was not registered. Good adherence is necessary to prevent CVD in FH-patients, and for these 8.3% completely non-adherent patients in our study the consequences can be fatal. Many had cholesterol levels as untreated FH-patients. Importantly, 25% of the patients off statin therapy had a history of a CV event.

The World Health Organization proposes that five dimension affects the patient's adherence; i) social and economic factors, ii) health care team and system-related factors, iii) condition-related factors, iv) therapy-related factors and v) patient-related factors (189). The reasons for not using statin therapy in our study can mainly be classified as patients-related factors (preference for herbal medicine and forgetting to renew prescription, not restarted statin therapy after pregnancy/breastfeeding and non-compliance) and therapy-related factors (adverse effects, not restarted statin therapy after pregnancy/breastfeeding). Adverse effects and lack of medication are known reasons for non-adherence among FH-patients (182). Moreover, some patients might have a weakened risk perception, leading to an absent understanding of the CV risk untreated FH entails and the importance of compliance towards the treatment. Others might deny the disease, and cannot put up with the increased CVD risk. It is also conceivable that the health care team and system-related factors are partly to blame. Is there suboptimal communication between the patient and the doctor? Are the doctors not

skilled enough to explain why the patients need statin therapy? Does the doctor blame the patient for the non-adherence? Further, social and economic factors might play a role in the decision about statin therapy. If the patients are aware of that statins might give adverse effects, either from the patient's acquaintance or from publicity in media, it is easy to apply these finding to them self. It is unlikely that statins constitute any meaningful excessive additional cost for these patients, as they are entitled to get the medication on blue prescription (124). Most likely the fundamental reasons for refraining statin therapy is a mixture of several of these factors. Nevertheless, it is important that the doctor takes the patient's thoughts and concerns into account, and explains the importance of statin therapy to prevent CVD.

Lipid values

Pre-treatment TC and LDL-C was lowered with 42.9% and 47.9% to V1. Further, TC and LDL-C was lowered with 8.9% and 15.8% from V1 to V3, respectively. Thus, our study shows that in a real life setting it was possible to achieve a 63.7% reduction in LDL-C after a treatment period of eight to ten years. This is important information useful for health economics to better understand the role of PCSK9 inhibitors in the current therapeutic landscape. Until V1, this reduction was mostly attributable to the statin therapy. But diet and lifestyle modification might also have contributed. From V1 to V3, other LLMs like ezetimibe and resins contributed to the further reduction. As a consequence of the reduced levels of TC and LDL-C, nonHDL-C was reduced. The treated lipid values at V3 are in line with other similar studies. In these studies LLM also resulted in a major reduction of pre-treatment cholesterol levels (164, 182).

As we included patients off statin therapy at V3, we might have underestimated the effect of the lipid lowering treatment given full compliance. By excluding the 13 patients who were off statins, we got a more precise picture of the attainment with the treatment. The lipid values at V3 became somewhat better, with mean values of TC at 4.9 mmol/L (95% CI: 4.7, 5.0 mmol/L), LDL-C at 3.0 mmol/L (95% CI: 2.9, 3.1 mmol/L) and ApoB at 1.0 g/L (95% CI: 1.0, 1.1 g/L). The other lipid values remained unchanged.

Although TC and LDL-C was reduced in a significant manner, only 40% met the treatment target of a LDL-C <2.5 mmol/L at V3. This indicates that despite aggressive treatment in the majority of the patients they were still not sufficiently treated. However, compared to other

similar studies, we had a higher proportion meeting the treatment target. In a study from the Netherlands, 21% had an LDL-C <2.5 mmol/L (164), however a lower proportion was treated with maximum statin dose than our population. In the SAFEHEART-trial, were 71.8% of the FH-cases where at maximum LLM, only 11% achieved an LDL-C <2.5mmol/L. A treatment target of LDL-C <2.5 mmol/L might be ideal in healthy young FH adults, but it is questionable whether it is realistic without use of PCSK9-inhibitors. Although the treatment targets are not met, the CV risk is substantially reduced. Versmissen et al showed that among FH-patients free from CVD relatively modest doses of statins reduced the risk of CHD by about 80% (102). Since increased LDL-C is the cause of the disease we can assume that the CVD-risk is greatly reduced among the patients in our study despite failure to meet the treatment target for many.

Further, 93.7% of those at very high CV risk at V3 were not sufficiently treated, and did not meet the target of an LDL-C <1.8 mmol/L. Possible explanations of the low achievement of the treatment targets will be further discussed.

A higher proportion of patients treated with a high intensity statin met the treatment target of an LDL-C <2.5 mmol/L, than patients treated with a moderate intensity statin (45.0% vs. 22.2%), indicating that a number of the patients treated with a moderate intensity statin might expect an additional LDL-C lowering effects of changing to a statin with higher potency. However, despite treatment with a high intensity statin, no higher proportion of patients meeting the secondary treatment target of an LDL-C <1.8 mmol/L was observed compared to moderate intensity statin therapy. It may be speculated if patients with a reduced LDL-C lowering response to statins may have particular mutations. There are five classes of LDL-R gene mutations, where the first two are receptor negative mutations, leading to no production of the LDL-R. The remaining classes are receptor defective mutations, where the receptor is produced but exerts a reduced activity (190). Different mutations are associated with variances in pre-treatment LDL-C levels (191) and LDL-C lowering response to statins (192). Mutations leading to more functional receptors are “milder”, for example class V compared to class II (190). Since we did not register class of mutations in our study, we cannot investigate if there is differential response to the drug therapy based on the mutations. Further, genetic polymorphisms of the drug metabolism might result in different effects of statins (193). Furthermore, non-adherence towards the treatment could be a factor decreasing the efficacy of lipid lowering treatment.

Using two or more LLMs may compensate for the insufficient effects of statins. One third of the patients treated with only one or no LLM had an LDL-C <2.5 mmol/L, whereas half of the patients treated with two LLMs met the target. However, this trend was not observed for achievement of an LDL-C <1.8 mmol/L. When comparing treatment with three LLMs against two or less LLMs, no difference in the achievement of either LDL-C <2.5 mmol/L or <1.8 mmol/L was seen. These findings suggest that FH-patients have difficulties achieving a low cholesterol levels even when treated with aggressive LLM. Further the finding of that among 18.4% of the patients who did not receive changes in the medication at V3 due to maximum treatment with triple LLM, implicates the need for even more potent lipid lowering therapy.

During the study period TG increased with 16.7%, explaining why TC and LDL-C did not decrease in the same manner. In addition, apoB increased with 10%. A concomitant decrease in LDL-C and increase in TG and ApoB, in addition to an elevated nonHDL-C indicates an increased level of small dense LDL- and remnants particles. These particles contain apoB and are highly atherogenic (194). Resins have a slight TG-raising effect due to an increased synthesis of VLDL (195, 196); however the observed increase in TG was not associated with resin therapy.

Metabolic risk profile

Fasting glucose and HbA1c increased with 10.5% and 7.0%, respectively, during the study period resulting in that on average the FH-population was classified as pre-diabetic at V3. However, without a control group it is difficult to interpret that many developed reduced glucose tolerance and insulin resistance. Colesevelam has a modest lowering effect on fasting glucose and HbA1c (197). The observed increase in fasting glucose and HbA1c could have been lower in patients treated with colesevelam, but this was not the case in the present study. Further, it is conceivable that muscle pain as an adverse effect, could lead to reduced physical activity, and further an increased HbA1c, as regular physical activity affects glycaemic control positively (198). However, the increase in HbA1c was not different for patients with or without muscular adverse effects or adverse effects in general.

Further, we observed an increase in weight and BMI for both genders and in WC among men from V1 to V3. Findings from epidemiologic studies shows that in developed countries aging up to 50-60 years of age is associated with weight gain (160, 199). The same applies to the prevalence of MetS (200). At V3, approximately 30% was diagnosed with MetS, which is

similar to what was found in a cross-sectional analysis of age-matched participants from HUNT 2 (200). Although this could be seen at as a normal development, it is concerning in this population as presence of MetS places the FH-patient at a higher CV risk (201, 202). The increase in WC was about 6 cm among men; in comparisons Cerhan et al found that every 5% increase in WC was associated with a 7% increase in all-cause mortality among men. However, caution should be made when interpreting the finding of an increased WC, as comparisons of WC at V1 and V3 was only carried out in 22 men and 20 women, due to a heavy load of missing in WC at V1. The comparisons of WC between men at V1 and V3 (table 9c) and V2 and V3 (table 9b) yielded different means at V3 than the mean for the total sample of 74 men at V3 (table 1). There are also similar findings among women. Thus, the increase in WC might have been overestimated due to that those who measured WC at V1 were the ones whit the largest increase during the study period.

The prevalence of MetS was somewhat similar when using the IDF and NCEP ATP III criteria, with a slightly higher proportion diagnosed with NCEP ATP III. As the IDF criteria require presence of a larger WC it was not possible to set the diagnosis for four patients, since measures of WC was missing and presence of other criteria was sufficiently to set the diagnosis if the WC was high. Thus we can assume that both definitions diagnose MetS to the same extent, given that all criteria are measured.

On average the patients had a WC above the threshold set by the NCEP ATP III. Several were classified as having abdominal obesity, especially among the women. As the diagnosis of MetS is based on the presence of several metabolic risk factors not only abdominal obesity, a number of these patients were classified as non-metabolic. An increased WC could be interpreted as a sign of an unhealthy development towards the MetS, and effort should be made to prevent this. Presence of abdominal obesity gives an unhealthy impression of the body composition. However, we did not measure hip circumference and calculated waist/hip-ratio. Waist/hip-ratio is an estimate of the amount of visceral fat relative to the amount of subcutaneous fat, and shows a stronger relation to risk of MI than WC alone (203). Measuring of waist/hip-ratio could have given a better impression of the body composition, especially among women as men are more prone to accumulate visceral fat (204). Further, waist/hip-ratio was shown to be a better predictor of MI-risk in the INTERHEART study (203).

The increase in TG and ApoB can be considered as a result of the abdominal obesity and development of insulin resistance. In addition, it is often accompanied by a decrease in HDL-

C, which we did not observe among our patients. In a study with insulin-sensitive, insulin-resistant and untreated subjects with DMT2, insulin resistance had profound effects on lipoprotein size and concentrations for VLDL, LDL and HDL. Compared with insulin-sensitive subjects, subjects with insulin resistance and DMT2 showed a 2- to 3-fold increase in concentrations of VLDL and a concomitant increase in TG. Concentration of LDL-particles increased in addition to number of small LDL-particles (205). It is therefore likely to assume that the increase in TG and apoB in our population could be attributable to the development of insulin resistance.

The concerning finding of that FH-patients, who receive regular follow-up with health professionals, develop MetS to the same extent as the general population might imply that FH-patients receive treatment for their FH, but the treatment of MetS could be improved. Hypertension is treated, as seen out of the proportion treated with antihypertensive medications and the average BP in the FH-population. On the other hand, abdominal obesity, elevated TG and insulin resistance is not the main focus in the FH-treatment. Little is known about what risk presence of MetS constitute in FH-patients. As mentioned in section 1.3.4, presence of MetS is associated with a 2-fold increased CV risk in the general population (65), and we can assume that it is at least as applicable to FH-patients. It is also possible that the risk is multiplied together with the risk FH constitutes. This should be evaluated in larger prospective studies. Nevertheless, presence of MetS is a CV risk factor, and effort should be made to prevent the development towards a metabolic profile. Regular monitoring of the factors involved in the MetS, as well as taken action when a negative trend is seen is important. Presence of MetS indicates a more aggressive modification and treatment of risk factors (10).

Diet and lifestyle

From V1 to V3 SmD-score increased, and a higher proportion of the patients had SmD-scores classified in the top category, which might be explained by the increased score in the meat- and vegetable-category. Although the SmD-score was relatively high, the intake of particularly foods could have been better. We observed an increase in the intake of vegetables from V1 to V3 and of fruit and vegetables together from V2 to V3, which is a development in the right direction. However, the intake of fruit and vegetables may advantageously be increased. We recommend an intake of five portions fruit and vegetables daily, were

vegetables constitute one half (133). No more than one third had an intake above four portions a day, and how many of those who had an intake of five portions a day are probably less. By increasing the intake of fruit and vegetables, the intake of fibre, vitamins and minerals consequently increases. In addition to having a hypocholesterolemic effects, fibre increases satiety, which could have beneficial effects considering counteracting weight gain and improving weight loss (206). Adding fibre to the diet slows the increase in glucose levels and consequently the secretion of insulin, preferably among individuals with DM or impaired glucose tolerance (206). Furthermore, by increasing the intake of fruit and vegetables other less favourable foods, like cakes, snacks and candy, can be replaced and provide further beneficial effects. However, the merging of the different SmD-variants considering the questions about fruit and vegetables could have biased our results. To get enough data on intake of fruit and vegetables, we had to merge the separate questions about intake of fruit and vegetables, leading to that 10% of those eating less than one fruit and less than one vegetable a day was classified as having an intake of two to four portions of fruit and vegetable together.

Compared to V2 the fish-intake was higher at V3, but no difference between V1 and V3 was observed. The intake of fish could generally been higher. Fatty fish is a good source of marine omega-3 fatty acids. It has been alleged that omega-3 fatty acids has cardioprotective effects, especially anti arrhythmic effects (207). However as mentioned earlier, recent research has questioned these findings (174-176). Though, half of the patients used omega-3 supplements on a regular basis at V3, we did observed a markedly decrease in the use of omega-3 capsules from V1 to V3 which might can be attributable to the loss of credibility of omega-3. Nevertheless, both lean and fatty fish are low in saturated and high in unsaturated fat, and should be eaten regularly as a part of a cardioprotective diet.

It is possible to gain weight even with a relatively high SmD-score. Vegetable oils, nuts and fatty fish are important components of a cardioprotective diet, but they contain high amounts of fat and are energy-dense. A long-term unrestricted intake of such foods can potentially lead to weight gain. A high intake of sugar-sweetened beverages and energy-dense foods without compensatory high energy expenditure, often leads to weight gain and overweight (134) . We did not evaluate intake of snacks, sugar-sweetened beverages and candy as individual subgroups. An increase in the intake of such foods might be masked by an improvement in other non-registered subgroups, as whole grain bread. However, based on the practical

experience from the dietary consultation with the patients the impression is that most patients reported to have a relatively reasonable intake of these foods during the whole study period.

In SmD most attention is given to the intake of amount and type of fat, since restriction of saturated fat is the main focus in the dietary treatment of FH. Less attention is given to sodium intake. A high sodium intake does not affect the cholesterol level, however it is associated with higher BP levels (134). As hypertension is a CV risk factor, it is important to prevent the development and treat established hypertension. Elevated BP is also an important factor in the MetS. Since MetS is present in many FH-patients, a reduced sodium intake should also be in focus in the dietary counselling together with a reduced fat intake.

When it comes to physical activity, not more than half of the patients met the recommendation of 150 minutes weekly with physical activity at all visits. Probably the proportion was even smaller. As the SmD-results was relatively good, it is reasonable to assume that the relatively low level of physical activity partly can explain the weight gain and the development of metabolic traits observed in our population. In addition to have cardioprotective effects (80), moderate aerobic exercise on a regular, long-term basis has profound effects on glucose metabolism and insulin sensitivity (83). Engaging in regular physical activity is also associated with reduced amount of abdominal fat (208). Diet is already given much attention in the treatment of FH, but it is also important to focus on the importance of regular physical activity to prevent CVD and MetS.

During the study period we did not observe any significant changes in smoking habits. Even though national anti-smoking campaigns have been carried out several times during the last decades, and doctors and clinical dieticians at the Lipid Clinic has informed about the severely increased CV risk resulting from smoking, approximately 14% were still classified as smokers at V3. Emphasis should be made in smoking cessation on the remaining smokers.

We cannot rule out that the reported dietary and lifestyle results are biased. As mentioned earlier, pleasing bias can occur in the consultations between the patient and a clinical dietician/doctor. Further, the focus on only dairy products, meat, fish and fruit and vegetables may have led to that we missed valuable information about the intake of other foods that might have affected the increase in SmD-score and improvement in the category distribution. Physical activity and intake of fruit may vary with the seasons of the year. However, V3 part I was carried out during the fall and winter season, while V3 part II mainly was carried out

during the late winter and fall season, and thus counterbalanced each other. Thus, we choose to interpret the increase in SmD-score as an improvement in the patient's dietary habits. Each time they fill out SmD, they learn more about the components in a cardioprotective diet. Regular monitoring and a greater number of counselling sessions enhance the compliance towards the given advices (209). Over the years they have become more skilled in making cardioprotective food choices.

Patient's preferences concerning the treatment

The patient's preference form was only collected at V1 and V3. During the study period, most of the patients still partly or fully agreed to the statement "a healthy lifestyle is as important as medicines" and "I prefer to have as low cholesterol as possible". Further, one question showed a significant change from V1 to V3. At V1, 61.7% stated that they fully or partly disagreed to whether they wanted little side effects rather than low cholesterol; whereas 20.0% stated that they were fully or partly agree to the statement. At V3, 40.8% fully or partly disagreed with the statement, while 33.3% fully or partly agreed, meaning that a larger proportion of the patients expressed having a higher preference for not having adverse effects than a low cholesterol level at V3. This could potentially lead to that patients choose to reduce their dosage or cessation of LLM if they feel any discomfort that could be related to their medication.

5.2.2 Comparisons of patients with and without CVD at V3

Despite the fact that the CHD mortality among FH-patients markedly decreased after the introduction of statins (102, 210), CHD mortality is still high (22). Investigating if the patients with CVD differ from those without CVD is of highly interest in order to consider which preventive actions to focus on, both to prevent incident and recurrent CVD.

The rate of CVD in the present study is consistent with findings from a retrospective assessment of FH-patients in Dutch lipid clinics. Further, they showed that male gender, smoking, low HDL-C and high Lp(a) appeared to be significant risk factors for CVD, somewhat consistent with our findings (29).

Age and gender characteristics

Patients with CVD at V3 were significantly older than patients without CVD, and most of them had experienced a coronary event. These findings are similar to findings in a study of Mundal et al. using hospital discharges from 1994-2009 to reflect the burden of CVD morbidity among FH-patients registered in the National Unit for Cardiac and Cardiovascular Genetics (11). FH-patients were first time hospitalised for CVD at a mean age at 45.1 years, consistent with our results with an age of 45.7 years at first-time CV event. In comparison, the mean age for first CVD event was 64.9 years in the general population in the same time period (211).

Not surprisingly, there was a predominance of men among patients with CVD, since male FH patients tends to have an accelerated CHD risk compared to both the general population and women with FH (212). As the non-CVD on average was younger and had a higher proportion of women, we can assume that the proportion of women with CVD will increase in about ten to 15 years.

Patients with CVD were older at FH-diagnosis compared to patients without CVD, and were about the same age as Mundal et al. patient population (11). Seen in context with the higher pre-treatment values of TC in the CVD-group, this might be indicative of an increased accumulated cholesterol burden and consecutively a very high risk of CVD (9). These findings underscore the importance of early detection and treatment of FH.

The patients without CVD were on average older than the mean age at first CV event in the CVD-group, which may indicate that other factors protect the non-CVD group from developing CVD, for example a more favourable CV-risk profile during their lifetime.

Presence of CVD at time of death

Mundal et al. found in a registry-based study on mortality among Norwegian FH-patients that CVD was responsible for 46% of all deaths from 1992 to 2010 (22). In our study, CVD was established among 50% of the patients who died, and it is likely that CVD was the cause of death in many cases. As Mundal et al. pointed out, CVD was responsible for 37% of deaths in the Norwegian population in 2010, demonstrating that FH patients still have significantly increased CVD mortality compared with the general Norwegian population.

Presence of metabolic risk factors

Patients with CVD had more metabolic risk factors at V3 compared to those free of CVD. On average, patients with CVD had levels of fasting glucose and HbA1c well within the criteria of prediabetes (85). Furthermore, higher WC among men, higher levels of TG and tendency towards lower levels of HDL-C in both genders with CVD, resulted in more than twice as many patients with CVD having MetS compared to the non-CVD group. This finding is concerning, as patients with FH and established CVD already has a high risk of recurrent CV events and increased CV mortality (11). Presence of MetS and metabolic risk factors will further increase the CV risk to an even higher extent (65).

The finding of a higher occurrence of abdominal obesity among men with CVD compared to men without CVD supports the hypothesis of that accumulation of visceral fat increases the CV risk. The presence of abdominal obesity was apparent in both women with and without CVD. Likely this could be affected by the lack of waist/hip-ratio as mentioned in section 5.2.3. If we had measured waist/hip-ratio, we might detect a difference between women with and without CVD.

Lipid values and medications

Remarkably, we found no differences between the two groups concerning values of TC and LDL-C at V3. Patients with established CVD have more stringent LDL-C targets to compensate for the excess CVD risk. Thus they need more aggressive lipid lowering treatment, which we observed as a higher proportion of the patients with CVD were treated with a high intensity statin. It is tempting to speculate if a model suggested by Nordestgaard et al could explain the reasons for not observing any differences in TC and LDL-C despite a more aggressive lipid lowering treatment in the CVD-group (9). The presence of one or more CV risk factors will increase the cholesterol burden and lead to a shift towards an earlier threshold for CHD. We found that patients with CVD had higher a higher proportion treated with antihypertensive medication, a higher proportion of males, and presence of metabolic risk factors leading to a higher proportion with MetS. In addition, patients with CVD had higher pre-treatment TC and were diagnosed and initiated treatment for FH around a decade later than the patients without CVD, suggesting that patients with CVD have a higher cholesterol burden. As mentioned earlier, different mutations in the LDL-R may affect the effectiveness of statin therapy. Thus, patients with established CVD might have a severer

mutation. Further, non-adherence towards the treatment could lead to a reduced LDL-C lowering effect. However, are patients with CVD non-adherent? These patients receive more frequently contact with doctors and take several medications daily than preferably healthy and asymptomatic patients. The probability of forgetting to take the LLM is assumed to be small. Moreover, if adherence to the treatment was low before the CV event, the CV event may have led to an increase in the understanding of the importance of being adherent. Nevertheless, three patients (6.1%) patients with CVD were not treated with statins, indicating that also this patient group are prone to be non-adherent.

Diet and lifestyle

There were no major findings concerning differences in the diet between patients with or without CVD, as both groups had a relatively cardioprotective diet. We used the SmD-results from V3, which were collected after the patients had experienced their CV event(s). If the patients with CVD had an unhealthier diet before the CV event(s), there is a chance that the incident affected the patient's diet towards a healthier direction. We could have conducted analyses of the dietary habits of patients with or without CVD at V1; however since around 20% had experienced one or more CV events prior to V1 we would still not fully avoided this problem.

Patients with CVD eat more fish than the patients without CVD. As mentioned, the CV event could have affected the patient's diet, and resulted in a higher intake of fish since fish is an important component of a cardioprotective diet. However, if the patients increased their intake of healthy foods as a consequence of the CV event, we could also expect that the intake of fruit and vegetables increased. Here we observed the opposite, with a higher intake of vegetables among the patients without CVD.

No differences were observed regarding physical activity, no more than half of the population met the recommendations of 150 min weekly. Physical activity is as least important in secondary prevention of CVD as in primary prevention (213). However, it should be emphasized that patients with CVD need guidance and individual adaption to exercise training from physiotherapists. Many of the patients experienced their CV event years ago, thus the motivation and drive to be physical active might be reduced. In addition, increasing age could have led to reduced amount of physical activity due to disability and occurrence of

other diseases. However, it is important that patients with CVD get reminded of the importance of being physical active to prevent recurrent CV events.

There was no difference in the proportion who reported to be current smokers, but a greater proportion of former smokers in the CVD-group than in the non-CVD-group (36.7% vs. 19.6%, respectively) were observed, reflecting that a higher proportion of patients with CVD had quit smoking. If the CV event itself of other factors led to the smoking cessation, is uncertain. Nevertheless, it is positive that some patients with CVD choose to quit smoking. Beneficial effects of smoking cessations on CV risk factors are observed within a year (214). For light smokers, the excess CV risk dissipates within five years. In contrast, moderate and heavy smokers have an excess CV risk for decades after cessation (53). As smoking greatly increases the CV risk, patients with FH should be strongly encouraged not to start smoking in the first place and effort should be made to motivate the remaining patients to quit, both those with and without CVD.

6 Conclusion

First, in the present study we found for the whole FH-population that:

1. The FH-patients was clinically diagnosed late, on average in their early thirties.

2. The vast majority of the patients were treated with a high intensity statin and/or ezetimibe in combination with a statin. 27.6% was treated with colesevelam, where all patients except one patient used it as a triple LLM. Few patients used high dose omega-3 or PCSK9-inhibitors. 29.5% used antihypertensive medication, and 12.2% was treated with glucose lowering medications. The patients had approximately been treated with statins the last 19 years, which might have led to somewhat increased occurrence of DM.

3. Statin and colesevelam was the LLMs giving adverse effects, where around 30% of the patients experienced adverse effects from these two LLMs. The adverse effects from statins were mostly muscular, while from colesevelam all were gastrointestinal.

4. 13 patients, with a predominance of women, were off statin therapy, where adverse events or scepsism toward statins were mostly reported as reasons for not using statins. Other reported reasons were delayed start of statin therapy after pregnancy/breastfeeding and forgetfulness. TC and LDL-C ranged from 5.2-12.0 mmol/L and 2.9-9.4 mmol/L, respectively. Three of the patients had established CVD.

5. On average, the FH-patients had a TC and LDL-C of 5.1 mmol/L and 3.2 mmol/L, respectively. Levels of HDL-C and TG were within the normal range. Despite aggressive treatment, only 40% met the primary treatment target of an LDL-C <2.5 mmol/L. The secondary treatment target of an LDL-C <1.8 mmol/L was only met by 6.3% of the patients with established CVD, DM or who was diagnosed after 40 years of age.

6. Fasting blood glucose and HbA1c was slightly elevated with average levels of 5.7 mmol/L and 5.8%, respectively, which is in the lower range of the criteria of pre-diabetes.

7. The FH-patients was slightly overweight, and 35.1% of the men and 53.0% of the women had abdominal obesity. MetS was present among approximately 30%, and several others were at risk for developing MetS.

8. The FH-patients had a relatively cardioprotective diet, reflected by a SmD-score in the upper end and a high proportion in the two top categories. The subgroup-results were mostly satisfactory, except that the consumption of fish, fruit and vegetables could have been somewhat higher. Further, most FH-patients had moderate alcohol intake. The amount of physical activity was somewhat low, where 51.3% was physical active in 30 minutes at least three times a week. Although smoking is a strong CV risk factor, 14.2% was smokers.

9. Most of the FH-patients considered a healthy lifestyle as important as LLM and wanted their cholesterol level to be as low as possible. However, 41% could not accept to have adverse effects in order to achieve a low cholesterol level.

Second, we measured changes from V1 to V3 in the FH-population, and found that:

10. It is possible to reduce TC and LDL-C to a great extent with aggressive lipid lowering treatment. In contrast, TG was slightly increased together with markedly increase in fasting glucose and HbA1c.

11. An unfavorable trend in the body size and composition was seen throughout the whole study period. WC increased considerable among men, and weight and BMI increased in both genders withthree3 kg and one unit, respectively.

12. SmD-score increased from V1 to V3 with nearly one point, and the proportion with a SmD-score in the lowest category was more than halved. Several small, but positive changes were observed during the study period, like a higher point-score for the intake of meat, fish, fruit and vegetables. No changes in amount of physical activity, smoking and alcohol consumption was observed. There was no difference in the proportion of smokers at the different visits, indicating that the patients who smoke were not willing or able to quit, or that the health professionals were not able to profoundly motivate them to smoking cessation.

13. The only change in the patient's preference was that a higher proportion of the patients expressed having higher preferences for not experiencing adverse effects than having a low cholesterol level at V3 compared to V1.

Last, by comparing patients with CVD against those without CVD we found that:

14. Patients with CVD were older at V3 and diagnosed with FH approximately 11 years later than patients without CVD. The patients got premature CVD with the age at first-time CV event of 45 years on average.

15. A significantly higher proportion among the patients with CVD was treated with a high intensity statin, triple LLM and antihypertensive medication. No difference in the use of two or more LLM, blood glucose lowering medication was seen.

16. Patients with CVD had 1.6 mmol/L higher pre-treatment levels than patients free from CVD. No difference in TC and LDL-C was seen at V3. Levels of TG, HbA1c and fasting glucose was higher among patients with CVD. On average the patients with CVD was classified as pre-diabetic.

17. Males with CVD had a higher WC and a higher proportion with abdominal obesity than males without CVD. Though a high proportion of women with CVD had abdominal obesity, the proportion was not significantly higher than the women without CVD. The increased WC and metabolic blood parameters and a higher proportion of patients with CVD treated with antihypertensive medication led to that around 50% of the patients with CVD was classified as having MetS. In comparison, the prevalence of MetS among patients without CVD ranged from 16.8% to 22.4% depending on the definition.

18. Both groups had a relatively cardioprotective diet, where patients without CVD had a higher intake of vegetables, and patients with CVD had a higher intake of fish. Both groups had a moderate intake of alcohol, and where physical active to the same extent. The amount of physical activity was disappointing; with only half of the patients in both groups were physical active in 30 minutes at least three times a week. The only lifestyle variable that differed between the two groups was the proportion of former smokers, which was significantly larger in the CVD-group.

7 Clinical implications and future perspectives

Our findings suggest that patients with FH have difficulties reaching the treatment targets in primary and secondary prevention despite aggressive lipid lowering treatment, which might implicate the need for more efficient therapies. Further, despite frequent contact with health professionals FH-patients tend to develop in a metabolic direction to the same extent as the general population. To avoid the development of MetS, it is important that health professionals' measures anthropometric data and initiates actions if an unfavorable trend are seen. Dietary counseling is an established and important part of the treatment provided at the Lipid Clinic, however focusing on the importance of physical activity and facilitate physical activity should also be emphasized. Also, emphasis to help and motivate smokers to quit smoking should be made. As patients with CVD were diagnosed with FH late in life and had higher pre-treatment TC early detection of FH and initiation of aggressive lipid lowering treatment and establishing healthy dietary and lifestyle habits is important. Systematic screening is critical to diagnose new FH-patients; where cascade screening is most cost-effective.

Future perspectives for the study are first of all to complete V3 for the whole study population, with a special emphasis to reach the patients who no longer are registered as patients at the Lipid Clinic. Since we were not able to investigate Lp(a) levels among the patients on average, and among patients with and without CVD, that should be in focus during the next visits of TTT-FH. Second, proceeding with new visits in the future is of interest. Further investigating of what distinguishes the patients with CVD from the patients without CVD is important to generate hypothesis, which further can be examined in larger observational studies of FH-patients. The risk MetS poses for FH-patients are uncertain, and should be subject to further research.

8 Conflict of interest

Kjetil Retterstøl has received honoraria for lectures from MSD, Pfizer, Mills, Da, Amgen and Sanofi.

Kjell-Erik Arnesen has received honoraria for lectures and advisory board fees from Sanofi, Amgen, Pronova, MSD, Pfizer, AstraZenica, Genzyme, Drammen Revmatikerforening, and the Norwegian Heart and Lung Patient Organization.

None of these companies or organizations has had impact on design of the protocol, planning and implementation of the study, or the content of this thesis.

References

1. World Health Organization. Cardiovascular diseases (CVDs): fact sheet. Geneva, Switzerland: World Health Organization; 2016 [updated 09.2016; cited 2016 03-15]. Available from: http://www.who.int/mediacentre/factsheets/fs317/en.
2. Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe--epidemiological update 2015. Eur Heart J. 2015;36(40):2696-705.
3. Sulo G, Igland J, Nygard O, Vollset SE, Ebbing M, Tell GS. Favourable trends in incidence of AMI in Norway during 2001-2009 do not include younger adults: a CVDNOR project. European journal of preventive cardiology. 2014;21(11):1358-64.
4. Folkehelseinstituttet. Folkehelserapporten 2014: Helsetilstanden i Norge www.folkehelseinstituttet.no: Folkehelseinstituttet; 2015.
5. Morita SY. Metabolism and Modification of Apolipoprotein B-Containing Lipoproteins Involved in Dyslipidemia and Atherosclerosis. Biol Pharm Bull. 2016;39(1):1-24.
6. Lusis AJ, Mar R, Pajukanta P. Genetics of atherosclerosis. Annual review of genomics and human genetics. 2004;5:189-218.
7. Kumar V, Robbins SL, Abbas AK, Aster JC. Robbins basic pathology. 9th ed. ed. Philadelphia, Pa: Elsevier/Saunders; 2013.
8. Ose L. Müller-Harbitz' sykdom - familiær hyperkolesterolemi. Tidsskr Nor Lægeforen 2002;122:924-5.
9. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478-90a.
10. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S1-8.
11. Mundal L, Veierod MB, Halvorsen T, Holven KB, Ose L, Iversen PO, et al. Cardiovascular disease in patients with genotyped familial hypercholesterolemia in Norway during 1994-2009, a registry study. European journal of preventive cardiology. 2016.
12. Krogh HW, Mundal L, Holven KB, Retterstol K. Patients with familial hypercholesterolaemia are characterized by presence of cardiovascular disease at the time of death. Eur Heart J. 2015.
13. Gidding SS, Ann Champagne M, de Ferranti SD, Defesche J, Ito MK, Knowles JW, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. Circulation. 2015;132(22):2167-92.
14. Goldstein JL, Brown MS. Familial hypercholesterolemia: identification of a defect in the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity associated with overproduction of cholesterol. Proc Natl Acad Sci U S A. 1973;70(10):2804-8.
15. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol. 2009;29(4):431-8.
16. National Center for Biotechnology Information ClinVar. Search results: LDLR gene: National Center for Biotechnology Information, ClinVar; 2016 [cited 2016 08-10]. Available from: http://www.ncbi.nlm.nih.gov/clinvar/?term=LDLR%5Bgene%5D.
17. Vogt A. The genetics of familial hypercholesterolemia and emerging therapies. Appl Clin Genet. 2015;8:27-36.

18. Vallejo-Vaz AJ, Kondapally Seshasai SR, Cole D, Hovingh GK, Kastelein JJ, Mata P, et al. Familial hypercholesterolaemia: A global call to arms. Atherosclerosis. 2015;243(1):257-9.
19. Heiberg A, Berg K. The inheritance of hyperlipoproteinaemia with xanthomatosis. A study of 132 kindreds. Clin Genet. 1976;9(2):203-33.
20. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. Eur Heart J. 2016;37(17):1384-94.
21. Nasjonal kompetansetjeneste for familiær hyperkolesterolemi. Hjelp oss å finne alle! Oslo, Norway: Nasjonal kompetansetjeneste for familiær hyperkolesterolemi; 2015 [updated 21.09.2016; cited 2016 10-26]. Available from: http://nktforfh.no/kampanje/hjelp-oss-a-finne-alle/.
22. Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierod MB, et al. Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992-2010. J Am Heart Assoc. 2014;3(6):e001236.
23. Statistisk sentralbyrå. Nøkkeltall for befolkning Statistisk sentralbyrå: Statistisk sentralbyrå; 2016 [updated 28.10.2016; cited 2016 11-01]. Available from: https://www.ssb.no/befolkning/nokkeltall.
24. Neefjes LA, Ten Kate GJ, Rossi A, Galema-Boers AJ, Langendonk JG, Weustink AC, et al. CT coronary plaque burden in asymptomatic patients with familial hypercholesterolaemia. Heart. 2011;97(14):1151-7.
25. Narverud I, Retterstol K, Iversen PO, Halvorsen B, Ueland T, Ulven SM, et al. Markers of atherosclerotic development in children with familial hypercholesterolemia: a literature review. Atherosclerosis. 2014;235(2):299-309.
26. Kusters DM, Wiegman A, Kastelein JJ, Hutten BA. Carotid intima-media thickness in children with familial hypercholesterolemia. Circ Res. 2014;114(2):307-10.
27. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016.
28. de Sauvage Nolting PR, Defesche JC, Buirma RJ, Hutten BA, Lansberg PJ, Kastelein JJ. Prevalence and significance of cardiovascular risk factors in a large cohort of patients with familial hypercholesterolaemia. J Intern Med. 2003;253(2):161-8.
29. Jansen AC, van Aalst-Cohen ES, Tanck MW, Trip MD, Lansberg PJ, Liem AH, et al. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: data in 2400 patients. J Intern Med. 2004;256(6):482-90.
30. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.
31. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421.
32. McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet. 2008;372(9634):224-33.
33. Walldius G, Jungner I. The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy--a review of the evidence. J Intern Med. 2006;259(5):493-519.

34. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370(9602):1829-39.
35. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol. 2012;60(25):2631-9.
36. Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015;385(9976):1397-405.
37. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-90.
38. Toth PP, Barter PJ, Rosenson RS, Boden WE, Chapman MJ, Cuchel M, et al. High-density lipoproteins: a consensus statement from the National Lipid Association. J Clin Lipidol. 2013;7(5):484-525.
39. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49-73.
40. Bhatt A, Rohatgi A. HDL Cholesterol Efflux Capacity: Cardiovascular Risk Factor and Potential Therapeutic Target. Current atherosclerosis reports. 2016;18(1):2.
41. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012;380(9841):572-80.
42. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, et al. Mendelian randomization of blood lipids for coronary heart disease. Eur Heart J. 2015;36(9):539-50.
43. Briel M, Ferreira-Gonzalez I, You JJ, Karanicolas PJ, Akl EA, Wu P, et al. Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. BMJ. 2009;338:b92.
44. Rader DJ, Hovingh GK. HDL and cardiovascular disease. Lancet. 2014;384(9943):618-25.
45. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384(9943):626-35.
46. Nordestgaard BG, Tybjaerg-Hansen A, Lewis B. Influx in vivo of low density, intermediate density, and very low density lipoproteins into aortic intimas of genetically hyperlipidemic rabbits. Roles of plasma concentrations, extent of aortic lesion, and lipoprotein particle size as determinants. Arterioscler Thromb. 1992;12(1):6-18.
47. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007;115(4):450-8.
48. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk. 1996;3(2):213-9.

49. Jorgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjaerg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. Eur Heart J. 2013;34(24):1826-33.
50. Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet. 2010;375(9726):1634-9.
51. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. J Lipid Res. 2016;57(11):1953-75.
52. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302(4):412-23.
53. Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet. 2006;368(9536):647-58.
54. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol. 2014;34(3):509-15.
55. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004;43(10):1731-7.
56. Athyros VG, Katsiki N, Doumas M, Karagiannis A, Mikhailidis DP. Effect of tobacco smoking and smoking cessation on plasma lipoproteins and associated major cardiovascular risk factors: a narrative review. Curr Med Res Opin. 2013;29(10):1263-74.
57. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):953-62.
58. Matthews KA, Gump BB. Chronic work stress and marital dissolution increase risk of posttrial mortality in men from the Multiple Risk Factor Intervention Trial. Arch Intern Med. 2002;162(3):309-15.
59. Strike PC, Steptoe A. Psychosocial factors in the development of coronary artery disease. Prog Cardiovasc Dis. 2004;46(4):337-47.
60. Helsedirektoratet. Forebygging, utredning og behandling av overvekt og fedme hos voksne: nasjonale retningslinjer for primærhelsetjenesten. Oslo, Norge: Helsedirektoratet; 2010. Report No.: IS-1735.
61. Sobiczewski W, Wirtwein M, Jarosz D, Gruchala M. Superiority of waist circumference and body mass index in cardiovascular risk assessment in hypertensive patients with coronary heart disease. Blood Press. 2015;24(2):90-5.
62. Despres JP. The insulin resistance-dyslipidemic syndrome of visceral obesity: effect on patients' risk. Obes Res. 1998;6 Suppl 1:8s-17s.
63. Gruson E, Montaye M, Kee F, Wagner A, Bingham A, Ruidavets JB, et al. Anthropometric assessment of abdominal obesity and coronary heart disease risk in men: the PRIME study. Heart. 2010;96(2):136-40.
64. Reeder BA, Senthilselvan A, Despres JP, Angel A, Liu L, Wang H, et al. The association of cardiovascular disease risk factors with abdominal obesity in Canada. Canadian Heart Health Surveys Research Group. CMAJ. 1997;157 Suppl 1:S39-45.
65. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56(14):1113-32.

66. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206-52.
67. Norheim OF, Gjelsvik B, Kjeldsen SE, Klemsdal TO, Madsen S, Meland E, et al. Nasjonale retningslinjer for individuell primærforebygging av hjerte- og karsykdommer. Oslo: Helsedirektoratet; 2009. Report No.: IS-1550.
68. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112-23.
69. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.
70. Puddu P, Puddu GM, Zaca F, Muscari A. Endothelial dysfunction in hypertension. Acta Cardiol. 2000;55(4):221-32.
71. Hartley L, Igbinedion E, Holmes J, Flowers N, Thorogood M, Clarke A, et al. Increased consumption of fruit and vegetables for the primary prevention of cardiovascular diseases. The Cochrane database of systematic reviews. 2013;6:Cd009874.
72. Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, Bao W, et al. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. BMJ. 2014;349:g4490.
73. Alissa EM, Ferns GA. Dietary Fruits and Vegetables and Cardiovascular Diseases Risk. Crit Rev Food Sci Nutr. 2015:0.
74. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med. 1996;334(18):1150-5.
75. Virtamo J, Rapola JM, Ripatti S, Heinonen OP, Taylor PR, Albanes D, et al. Effect of vitamin E and beta carotene on the incidence of primary nonfatal myocardial infarction and fatal coronary heart disease. Arch Intern Med. 1998;158(6):668-75.
76. Roberts LJ, 2nd, Traber MG, Frei B. Vitamins E and C in the prevention of cardiovascular disease and cancer in men. Free Radic Biol Med. 2009;46(11):1558.
77. Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342(3):154-60.
78. Rapola JM, Virtamo J, Ripatti S, Huttunen JK, Albanes D, Taylor PR, et al. Randomised trial of alpha-tocopherol and beta-carotene supplements on incidence of major coronary events in men with previous myocardial infarction. Lancet. 1997;349(9067):1715-20.
79. Held C, Iqbal R, Lear SA, Rosengren A, Islam S, Mathew J, et al. Physical activity levels, ownership of goods promoting sedentary behaviour and risk of myocardial infarction: results of the INTERHEART study. Eur Heart J. 2012;33(4):452-66.
80. Physical Activity Guidelines Advisory Committee report, 2008. To the Secretary of Health and Human Services. Part A: executive summary. Nutr Rev. 2009;67(2):114-20.
81. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation. 2003;107(24):3109-16.
82. Palmefors H, DuttaRoy S, Rundqvist B, Borjesson M. The effect of physical activity or exercise on key biomarkers in atherosclerosis--a systematic review. Atherosclerosis. 2014;235(1):150-61.

83. Thompson PD, Crouse SF, Goodpaster B, Kelley D, Moyna N, Pescatello L. The acute versus the chronic response to exercise. Med Sci Sports Exerc. 2001;33(6 Suppl):S438-45; discussion S52-3.
84. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. The Cochrane database of systematic reviews. 2011(7):Cd001800.
85. Standards of medical care in diabetes--2011. Diabetes Care. 2011;34 Suppl 1:S11-61.
86. Helsedirektoratet. Diabetes - Nasjonal faglig retningslinje for diabetes. Oslo: Helsedirektoratet; 2016. Available from: https://helsedirektoratet.no/retningslinjer/diabetes.
87. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 2011;377(9765):557-67.
88. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.
89. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007;28(1):88-136.
90. Szuszkiewicz-Garcia MM, Davidson JA. Cardiovascular disease in diabetes mellitus: risk factors and medical therapy. Endocrinol Metab Clin North Am. 2014;43(1):25-40.
91. Leong DP, Smyth A, Teo KK, McKee M, Rangarajan S, Pais P, et al. Patterns of alcohol consumption and myocardial infarction risk: observations from 52 countries in the INTERHEART case-control study. Circulation. 2014;130(5):390-8.
92. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 2011;342:d671.
93. Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. BMJ. 2011;342:d636.
94. Holmes MV, Dale CE, Zuccolo L, Silverwood RJ, Guo Y, Ye Z, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ. 2014;349:g4164.
95. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(7):483-95.
96. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ. 2000;321(7255):199-204.
97. Nordestgaard BG, Zacho J. Lipids, atherosclerosis and CVD risk: is CRP an innocent bystander? Nutr Metab Cardiovasc Dis. 2009;19(8):521-4.
98. Berger JS, Jordan CO, Lloyd-Jones D, Blumenthal RS. Screening for cardiovascular risk in asymptomatic patients. J Am Coll Cardiol. 2010;55(12):1169-77.
99. Kappert K, Bohm M, Schmieder R, Schumacher H, Teo K, Yusuf S, et al. Impact of sex on cardiovascular outcome in patients at high cardiovascular risk: analysis of the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET). Circulation. 2012;126(8):934-41.

100. Dyngeland J. Hjerte- og karregisteret: rapport for 2014. www.fhi.no; 2015.
101. Selmer R, Lindman AS, Tverdal A, Pedersen JI, Njolstad I, Veierod MB. [Model for estimation of cardiovascular risk in Norway]. Tidsskr Nor Laegeforen. 2008;128(3):286-90.
102. Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ. 2008;337:a2423.
103. Ness GC, Zhao Z, Lopez D. Inhibitors of cholesterol biosynthesis increase hepatic low-density lipoprotein receptor protein degradation. Arch Biochem Biophys. 1996;325(2):242-8.
104. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol. 2003;92(2):152-60.
105. Asher J, Houston M. Statins and C-reactive protein levels. J Clin Hypertens (Greenwich). 2007;9(8):622-8.
106. Gerards MC, Terlou RJ, Yu H, Koks CH, Gerdes VE. Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain - a systematic review and meta-analysis. Atherosclerosis. 2015;240(2):415-23.
107. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med. 2011;365(22):2078-87.
108. Jukema JW, Bruschke AV, van Boven AJ, Reiber JH, Bal ET, Zwinderman AH, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). Circulation. 1995;91(10):2528-40.
109. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004;291(9):1071-80.
110. Simic I, Reiner Z. Adverse effects of statins - myths and reality. Curr Pharm Des. 2015;21(9):1220-6.
111. Armitage J. The safety of statins in clinical practice. Lancet. 2007;370(9601):1781-90.
112. Wang KL, Liu CJ, Chao TF, Huang CM, Wu CH, Chen SJ, et al. Statins, risk of diabetes, and implications on outcomes in the general population. J Am Coll Cardiol. 2012;60(14):1231-8.
113. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012;380(9841):565-71.
114. Backes JM, Kostoff MD, Gibson CA, Ruisinger JF. Statin-Associated Diabetes Mellitus: Review and Clinical Guide. South Med J. 2016;109(3):167-73.
115. Pandor A, Ara RM, Tumur I, Wilkinson AJ, Paisley S, Duenas A, et al. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. J Intern Med. 2009;265(5):568-80.
116. Mikhailidis DP, Sibbring GC, Ballantyne CM, Davies GM, Catapano AL. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. Curr Med Res Opin. 2007;23(8):2009-26.
117. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372(25):2387-97.
118. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008;358(14):1431-43.

119. Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. Ann Pharmacother. 2001;35(7-8):898-907.
120. Jones MR, Nwose OM. Role of colesevelam in combination lipid-lowering therapy. Am J Cardiovasc Drugs. 2013;13(5):315-23.
121. Insull W, Jr. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. South Med J. 2006;99(3):257-73.
122. Zhang XL, Zhu QQ, Zhu L, Chen JZ, Chen QH, Li GN, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med. 2015;13:123.
123. Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, et al. Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. Ann Intern Med. 2015;163(1):40-51.
124. Bogsrud MP, Holven KB, Johansen D, Øyri L. Veileder for utredning og behandling av familiær hyperkolesterolemi (FH) i primærhelsetjenesten. In: hyperkolesterolemi Nkff, editor. www.nktforfh.no: Nasjonal kompetansetjeneste for familiær hyperkolesterolemi; 2016.
125. Shafiq N, Singh M, Kaur S, Khosla P, Malhotra S. Dietary treatment for familial hypercholesterolaemia. The Cochrane database of systematic reviews. 2010(1):Cd001918.
126. Malhotra A, Shafiq N, Arora A, Singh M, Kumar R, Malhotra S. Dietary interventions (plant sterols, stanols, omega-3 fatty acids, soy protein and dietary fibers) for familial hypercholesterolaemia. The Cochrane database of systematic reviews. 2014;6:Cd001918.
127. Gylling H, Plat J, Turley S, Ginsberg HN, Ellegard L, Jessup W, et al. Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease. Atherosclerosis. 2014;232(2):346-60.
128. Hopkins PN. Familial hypercholesterolemia--improving treatment and meeting guidelines. Int J Cardiol. 2003;89(1):13-23.
129. Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. JAMA. 2003;290(4):502-10.
130. Hooper L, Martin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. The Cochrane database of systematic reviews. 2015(6):Cd011737.
131. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2010;7(3):e1000252.
132. Van Horn L, McCoin M, Kris-Etherton PM, Burke F, Carson JA, Champagne CM, et al. The evidence for dietary prevention and treatment of cardiovascular disease. J Am Diet Assoc. 2008;108(2):287-331.
133. Nasjonalt råd for ernæring. Kostråd for å fremme folkehelsen og forebygge kroniske sykdommer : metodologi og vitenskapelig kunnskapsgrunnlag. Oslo, Norge: Helsedirektoratet; 2011. Report No.: IS-1881.
134. Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. Circulation. 2011;123(24):2870-91.
135. Øyri L, Johansen D, Holven K, Bogsrud M, Ellingvål A, Strøm E. Kostholdsråd ved høye blodlipider - for deg med høyt kolesterol eller høye triglyserider. In: hyperkolesterolemi Nkff, editor. www.nktforfh.no: Nasjonal kompetansetjeneste for familiær hyperkolesterolemi; 2016.
136. Theuwissen E, Mensink RP. Water-soluble dietary fibers and cardiovascular disease. Physiol Behav. 2008;94(2):285-92.
137. Helsedirektoratet. Anbefalinger om kosthold, ernæring og fysisk aktivitet. Oslo, Norge.: Helsedirektoratet; 2014. Report No.: IS-2170.

138. Grosso G, Marventano S, Yang J, Micek A, Pajak A, Scalfi L, et al. A Comprehensive Meta-analysis on Evidence of Mediterranean Diet and Cardiovascular Disease: Are Individual Components Equal? Crit Rev Food Sci Nutr. 2015:0.
139. Menotti A, Kromhout D, Blackburn H, Fidanza F, Buzina R, Nissinen A. Food intake patterns and 25-year mortality from coronary heart disease: cross-cultural correlations in the Seven Countries Study. The Seven Countries Study Research Group. Eur J Epidemiol. 1999;15(6):507-15.
140. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779-85.
141. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368(14):1279-90.
142. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 2014;17(12):2769-82.
143. Eijsvogels TM, Molossi S, Lee DC, Emery MS, Thompson PD. Exercise at the Extremes: The Amount of Exercise to Reduce Cardiovascular Events. J Am Coll Cardiol. 2016;67(3):316-29.
144. Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. Hypertension. 2011;58(5):950-8.
145. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva: World Health Organization; 2010.
146. Van Gaal LF, Michiels JJ. Obesity, health issues, and cardiovascular disease. Semin Vasc Med. 2005;5(1):1-2.
147. Robinson JG, Goldberg AC. Treatment of adults with familial hypercholesterolemia and evidence for treatment: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S18-29.
148. Thorvall M. Treat To Target Familial Hypercholesterolemia: A prospective study on effects from maximal high intensive treatment. www.duo.uio.no: University of Oslo; 2014.
149. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502.
150. Findalen AM, Arsky GH, Helsedirektoratet. Kosthåndboken: veileder i ernæringsarbeid i helse- og omsorgstjenesten. Oslo: Helsedirektoratet; 2012.
151. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.
152. Svilaas A, Strom EC, Johansen SG, Vebenstad G, Svilaas T, Ose L. Assessment of dietary habits and life style. Tidsskr Nor Laegeforen. 2011;131(5):454.
153. Svilaas A, Strom EC, Svilaas T, Borgejordet A, Thoresen M, Ose L. Reproducibility and validity of a short food questionnaire for the assessment of dietary habits. Nutr Metab Cardiovasc Dis. 2002;12(2):60-70.
154. Hollan I, Meroni PL, Ahearn JM, Cohen Tervaert JW, Curran S, Goodyear CS, et al. Cardiovascular disease in autoimmune rheumatic diseases. Autoimmunity reviews. 2013;12(10):1004-15.

155. Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis. 2011;70(6):929-34.
156. Gades NM, Jacobson DJ, McGree ME, Lieber MM, Roberts RO, Girman CJ, et al. Dropout in a longitudinal, cohort study of urologic disease in community men. BMC Med Res Methodol. 2006;6:58.
157. Goldberg M, Chastang JF, Leclerc A, Zins M, Bonenfant S, Bugel I, et al. Socioeconomic, demographic, occupational, and health factors associated with participation in a long-term epidemiologic survey: a prospective study of the French GAZEL cohort and its target population. Am J Epidemiol. 2001;154(4):373-84.
158. Drevon CA, Blomhoff R, Bjørneboe GEA. Mat og medisin: nordisk lærebok i generell og klinisk ernæring. 5th ed. Kristiansand: Høyskoleforl.; 2007.
159. Pedersen JI. Grunnleggende ernæringslære. 2th ed. Oslo: Gyldendal akademisk; 2012.
160. Droyvold WB, Nilsen TI, Kruger O, Holmen TL, Krokstad S, Midthjell K, et al. Change in height, weight and body mass index: Longitudinal data from the HUNT Study in Norway. Int J Obes (Lond). 2006;30(6):935-9.
161. Alonso R, Andres E, Mata N, Fuentes-Jimenez F, Badimon L, Lopez-Miranda J, et al. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. J Am Coll Cardiol. 2014;63(19):1982-9.
162. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009;301(22):2331-9.
163. Nenseter MS, Lindvig HW, Ueland T, Langslet G, Ose L, Holven KB, et al. Lipoprotein(a) levels in coronary heart disease-susceptible and -resistant patients with familial hypercholesterolemia. Atherosclerosis. 2011;216(2):426-32.
164. Pijlman AH, Huijgen R, Verhagen SN, Imholz BP, Liem AH, Kastelein JJ, et al. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in The Netherlands. Atherosclerosis. 2010;209(1):189-94.
165. Mata N, Alonso R, Badimon L, Padro T, Fuentes F, Muniz O, et al. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). Lipids Health Dis. 2011;10:94.
166. Leren TP, Tonstad S, Ose L. [Genetic screening and treatment in familial hypercholesterolemia]. Tidsskr Nor Laegeforen. 2001;121(13):1635-6.
167. Birch LL, Davison KK. Family environmental factors influencing the developing behavioral controls of food intake and childhood overweight. Pediatr Clin North Am. 2001;48(4):893-907.
168. Birch LL, Fisher JO. Development of eating behaviors among children and adolescents. Pediatrics. 1998;101(3 Pt 2):539-49.
169. Mikkila V, Rasanen L, Raitakari OT, Pietinen P, Viikari J. Consistent dietary patterns identified from childhood to adulthood: the cardiovascular risk in Young Finns Study. Br J Nutr. 2005;93(6):923-31.
170. Molven I, Retterstol K, Andersen LF, Veierod MB, Narverud I, Ose L, et al. Children and young adults with familial hypercholesterolaemia (FH) have healthier food choices particularly with respect to dietary fat sources compared with non-FH children. Journal of nutritional science. 2013;2:e32.
171. Leren TP. Cascade genetic screening for familial hypercholesterolemia. Clin Genet. 2004;66(6):483-7.

172. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child-Parent Familial Hypercholesterolemia Screening in Primary Care. N Engl J Med. 2016;375(17):1628-37.
173. Beaumont JL, Carlson LA, Cooper GR, Fejfar Z, Fredrickson DS, Strasser T. Classification of hyperlipidaemias and hyperlipoproteinaemias. Bull World Health Organ. 1970;43(6):891-915.
174. Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012;367(4):309-18.
175. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010;122(21):2152-9.
176. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010;363(21):2015-26.
177. Stene LC, Strøm H, Gulseth HL. Folkehelserapporten 2014 - Diabetes i Norge: Folkehelseinstituttet; 2015 [updated 10.12.2015; cited 2016 11-10]. Available from: https://www.fhi.no/nettpub/hin/helse-og-sykdom/diabetes-i-norge---folkehelserappor/.
178. Cooper JG, Claudi T, Jenum AK, Thue G, Hausken MF, Ingskog W, et al. Quality of care for patients with type 2 diabetes in primary care in Norway is improving: results of cross-sectional surveys of 33 general practices in 1995 and 2005. Diabetes Care. 2009;32(1):81-3.
179. Stene LC, Midthjell K, Jenum AK, Skeie S, Birkeland KI, Lund E, et al. [Prevalence of diabetes mellitus in Norway]. Tidsskr Nor Laegeforen. 2004;124(11):1511-4.
180. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735-42.
181. Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JE, Shah T, et al. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. Lancet. 2015;385(9965):351-61.
182. Galema-Boers JM, Lenzen MJ, van Domburg RT, Roeters van Lennep J, van Bruchem-van de Scheur GG, Sijbrands EJ, et al. Predicting non-adherence in patients with familial hypercholesterolemia. Eur J Clin Pharmacol. 2014;70(4):391-7.
183. Saxon DR, Eckel RH. Statin Intolerance: A Literature Review and Management Strategies. Prog Cardiovasc Dis. 2016;59(2):153-64.
184. Strandberg TE, Pyorala K, Cook TJ, Wilhelmsen L, Faergeman O, Thorgeirsson G, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet. 2004;364(9436):771-7.
185. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22.
186. Rosenbaum D, Dallongeville J, Sabouret P, Bruckert E. Discontinuation of statin therapy due to muscular side effects: a survey in real life. Nutr Metab Cardiovasc Dis. 2013;23(9):871-5.
187. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012;97(11):3956-64.
188. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487-97.
189. World Health Organization. ADHERENCE TO LONG-TERM THERAPIES: Evidence for action. Geneva, Switzerland; 2003. Report No.: 92 4 154599 2.
190. Miltiadous G, Xenophontos S, Bairaktari E, Ganotakis M, Cariolou M, Elisaf M. Genetic and environmental factors affecting the response to statin therapy in patients with

molecularly defined familial hypercholesterolaemia. Pharmacogenet Genomics. 2005;15(4):219-25.
191. Gudnason V, Day IN, Humphries SE. Effect on plasma lipid levels of different classes of mutations in the low-density lipoprotein receptor gene in patients with familial hypercholesterolemia. Arterioscler Thromb. 1994;14(11):1717-22.
192. Heath KE, Gudnason V, Humphries SE, Seed M. The type of mutation in the low density lipoprotein receptor gene influences the cholesterol-lowering response of the HMG-CoA reductase inhibitor simvastatin in patients with heterozygous familial hypercholesterolaemia. Atherosclerosis. 1999;143(1):41-54.
193. Vermes A, Vermes I. Genetic polymorphisms in cytochrome P450 enzymes: effect on efficacy and tolerability of HMG-CoA reductase inhibitors. Am J Cardiovasc Drugs. 2004;4(4):247-55.
194. Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. Circulation. 2004;109(23 Suppl 1):Iii2-7.
195. Angelin B, Leijd B, Hultcrantz R, Einarsson K. Increased turnover of very low density lipoprotein triglyceride during treatment with cholestyramine in familial hypercholesterolaemia. J Intern Med. 1990;227(3):201-6.
196. Beil U, Crouse JR, Einarsson K, Grundy SM. Effects of interruption of the enterohepatic circulation of bile acids on the transport of very low density-lipoprotein triglycerides. Metabolism. 1982;31(5):438-44.
197. Ooi CP, Loke SC. Colesevelam for type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2012;12:Cd009361.
198. Mikus CR, Oberlin DJ, Libla JL, Taylor AM, Booth FW, Thyfault JP. Lowering physical activity impairs glycemic control in healthy volunteers. Med Sci Sports Exerc. 2012;44(2):225-31.
199. Rissanen A, Heliovaara M, Aromaa A. Overweight and anthropometric changes in adulthood: a prospective study of 17,000 Finns. Int J Obes. 1988;12(5):391-401.
200. Hildrum B, Mykletun A, Hole T, Midthjell K, Dahl AA. Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study. BMC Public Health. 2007;7:220.
201. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49(4):403-14.
202. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med. 2006;119(10):812-9.
203. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 2005;366(9497):1640-9.
204. Despres JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol. 2008;28(6):1039-49.
205. Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A, et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. Diabetes. 2003;52(2):453-62.
206. Slavin JL. Dietary fiber and body weight. Nutrition. 2005;21(3):411-8.
207. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002;105(16):1897-903.

208. Ohkawara K, Tanaka S, Miyachi M, Ishikawa-Takata K, Tabata I. A dose-response relation between aerobic exercise and visceral fat reduction: systematic review of clinical trials. Int J Obes (Lond). 2007;31(12):1786-97.
209. Gilboy MB. Multiple factors affect dietitians' counseling practices for high blood cholesterol. J Am Diet Assoc. 1994;94(11):1278-83.
210. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. Atherosclerosis. 1999;142(1):105-12.
211. Igland J, Tell GS, Ebbing M, Nygard O, Vollset SE, Dimoski T. CVDNOR Data and Quality Report: The CVDNOR project: Cardiovascular Disease in Norway 1994–2009. Description of data and data quality CVDNOR; 2013 [cited 2016 10-21]. Available from: http://cvdnor.b.uib.no/files/2013/08/CVDNOR-Data-and-Quality-Report1.pdf.
212. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-Term Risk of Atherosclerotic Cardiovascular Disease in US Adults With the Familial Hypercholesterolemia Phenotype. Circulation. 2016;134(1):9-19.
213. Swift DL, Lavie CJ, Johannsen NM, Arena R, Earnest CP, O'Keefe JH, et al. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. Circ J. 2013;77(2):281-92.
214. Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of smoking and smoking cessation on lipids and lipoproteins: outcomes from a randomized clinical trial. Am Heart J. 2011;161(1):145-51.

Appendices

Appendix 1 The Dutch Lipid Network Criteria diagnostic criteria of Familial hypercholesterolemia

Appendix 2 The doctors form

Appendix 3 Smart Diet versions from 2003, 2007 and 2009.

Appendix 4 Patient's preference form

Appendix 5 Written informed consent

Appendix 6 Approval by the Regional Ethical Committee for Medical Research

Appendix 1. The Dutch Lipid Network Criteria diagnostic criteria of Familial Hypercholesterolemia

Criteria	Points
Family history	
First-degree relative with known premature* coronary and vascular disease, OR first-degree relative with known LDL-C level above the 95th percentile.	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR children aged less than 18 years with LDL-C level above the 95th percentile.	2
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels (mmol/L)	
LDL-C ≥ 8.5	8
LDL-C 6.5-8.4	5
LDL-C 5.0-6.4	3
LDL-C 4.0-4.9	1
DNA-analysis	
Functional mutation in the LDL-R, apo B or PCSK9 gene	8
Diagnosis (based on the total number of points obtained)	
Definite FH	>8
Probable FH	6-8
Possible FH	3-5
Unlikely FH	<3

Appendix 2. The doctors form

SCREENINGNR: _____ INITIALER:_____ DATO_____

TTTFH: Visitt 3 SIDE 1

MEDIKASJON

Har det vært endringer i medikasjon siden forrige visitt: ☐ Ja ☐ Nei

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

Bivirkninger ved dagens lipidmidler: 1. sikkert, 2. sannsynlig, 3. mulig, 4. nei

Dagens medikament				Tidligere medikament			
	_____	_____	_____	_____	_____	_____	_____
Bivirkning 1-3	_____	_____	_____	_____	_____	_____	_____
Type, beskriv	_____	_____	_____	_____	_____	_____	_____

Øker du lipidmedisineringen for å oppnå behandlingsmål: 1. Ja 2. Nei

Grunnene til ikke å øke lipidmedikasjon:

1) Pasient vil ikke/ er skeptisk etc
2) Behandlingsmålet er nådd
3) Pga bivirkninger
4) Legen ser det an (kostsvikt, annen variasjon), nye prøver 6 uker
5) Legen vil ikke ut fra samlet vurdering (mulige bivirkn, interaksjonsfare, mange medisiner allerede, ikke alvorlig familierisiko, pasientens holdning etc)
6) Har maks tålbar medikasjon, eller maks av det som var før PCSK9-hemmer
7) Graviditetsønske
8) Annet beskriv _____

Hvordan endres lipidmedikasjon:

1) Øker dosen av samme statin statin_____ fra dose_____ til dose_____
2) Reduserer dose samme statin statin_____ fra dose_____ til dose_____
3) Bytter til sterkere statin fra statin_____ til statin_____
3) Bytter til svakere statin fra statin_____ til statin_____
3) Legger til ezetimibe
4) Legger til colesevelam
5) Legger til PCSK9-hemmer
6) Legger til Omacor
7) Legger til Niaspan
8) Legger til Inegy dose_____

Dato_____ Lege sign_____

TTTFH: Visitt 3 SIDE 2

Pasienten har *ingen* lipidmedikasjon på visitt 3

Medikament ikke brukt	Grunnen til det	Avsluttet når dag/mnd/år		Fortsatt uten
				☐
				☐
				☐

Pasienten har hatt lange *pauser* i lipidmedikasjon

Medikament ikke brukt	Grunn til det 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 pas til Lipidklinikken _____

	Resin hos barn	Statin	Dobbelmedik type	Trippelmedik type
Når startet lipidmedikasjon	_____	_____	_____ ☐ ☐	_____ ☐ ☐ ☐

Når avsluttet oppfølging_____

- Selv ikke ønsket oppfølging
- Ikke møtt ved flere innkallinger
- Avviklet av oss og oppfølges ved fastlege
- Avviklet av oss og oppfølges ved sykehus/Lipidklinikk
- Selv ikke ønsket pga annen alvorlig sykdom
- Død. Årsak_____

SCREENINGNR: _____ INITIALER:_____ DATO_____

TTTFH: Visitt 3 SIDE 3

ADVERSE EVENTS

Ingen medisinske hendelser siden forrige visitt: ☐

Bruk helst diagnoser, ikke individuelle symptomer, hvis mulig

Adverse event				
Startdato	(dd/mmm/åååå)	(dd/mmm/åååå)	(dd/mmm/åååå)	(dd/mmm/åååå)
Alvorlighet	☐ 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 Økt ☐ 2 Redusert ☐ 3 Stoppet midlertidig ☐ 4 Stoppet permanent	☐ 1 Økt ☐ 2 Redusert ☐ 3 Stoppet midlertidig ☐ 4 Stoppet permanent	☐ 1 Økt ☐ 2 Redusert ☐ 3 Stoppet midlertidig ☐ 4 Stoppet permanent	☐ 1 Økt ☐ 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?	☐ Ja ☐ Ukjent ☐ Nei- løst	☐ Ja ☐ Ukjent ☐ Nei- løst	☐ Ja ☐ Ukjent ☐ Nei- løst	☐ Ja ☐ Ukjent ☐ Nei- løst
Dato løst	_____ (dd/mmm/åååå)	_____ (dd/mmm/åååå)	_____ (dd/mmm/åååå)	_____ (dd/mmm/åååå)
Årsak AE 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 Kardio-vaskulær 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 siden forrige visitt: ☐ **Ja** ☐ **Nei (eget skjema**

SCREENINGNR: _____ INITIALER:_____ DATO_____

TTTFH: Visitt 3 SIDE 4

SOSIALT

Endringer siden forrige visitt: ☐ Ja ☐ Nei

Skoleelev ☐ Student/lærling ☐ Fulltids jobb ☐ Deltidsjobb ☐
Hjemmeværende ☐ Sykemeldt ☐ Attføring/rehabilitering etc ☐
Arbeidsledig ☐ Delvis uførepensjon ☐ Full uførepensjon ☐

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

KOST

Endringer siden forrige visitt: ☐ Ja ☐ Nei

Poeng Smart diet _____ KEF i dag ☐ Fått skriftlig materiale i dag ☐

RØYKING

Endringer siden forrige visitt: ☐ Ja ☐ Nei

Aldri røykt ☐ Tidligere røykt ☐ Startet første gang_____ Sluttet siste gang_____
Sigarett røyker ☐ Antall per dag_____
Pipe/cigarillos røyker ☐ Antall per dag_____

ALKOHOL

Endringer siden forrige visitt: ☐ Ja ☐ Nei

Enheter per uke_____

TRENING

Endringer siden forrige visitt: ☐ Ja ☐ Nei
Type_____ Tid per uke_____
Type_____ Tid per uke_____
Type_____ Tid per uke_____
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 ☐ Ja ☐ Nei

Hvis JA, hvilken prevensjon: Medikamentnavn/klasse Type reaksjon

_____ _____
_____ _____
_____ _____
_____ _____

TTTFH: VISITT3 SIDE 5

Hvis det er potensielt endpunkt, fyll ut:

SUBJECT NO.	INITIALS (F M L)	DATE OF VISIT (dd MMM yyyy)

POTENTIAL ENDPOINTS

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

☐ Suspected or Confirmed Non Fatal Acute MI	☐ Hospitalization with Primary Diagnosis of CHF
☐ Death - Coronary	☐ Cerebrovascular Event • Fatal stroke • Non-fatal stroke • TIA
☐ Death - Other	
☐ Coronary Revascularization Procedure • Coronary artery bypass graft (CABG) • PTCA (includes atherectomy and stent implantation) • Other coronary revascularization procedure	☐ First Diagnosis of PVD
	☐ Hospitalized PVD Event
☐ Documentated Angina	☐ Other Non-CHD Vascular Events

Date of Event: dd MMM yyyy

If hospitalized, check one:

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

Specify site:* _____

☐ Admitted to:*

_____

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

Admission Date: dd MMM yyyy

Discharge Date: dd MMM yyyy

Date: dd MMM yyyy | Investigator's Signature: _____ | Monitor: _____

SmartDiet

Navn: .....

Fødselsdato: .....

Dato for besvarelsen:.....

20 spørsmål om ditt kosthold og din livsstil

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 .....

De gode rådene finner du her

Mettet fett er kolesterøkende. Reduser derfor inntaket av matvarer med mye mettet fett. Velg i stedet matvarer med mye umettet fett som kan senke kolesterolet.

Drikk mager melk, 1/2 liter skummet, søt eller sur, daglig. Dersom du ikke drikker melk daglig, kan det føre til et for lavt inntak av kalsium.

Alle fløte- og rømmetyper inneholder mye mettet fett og anbefales ikke i hverdagskostholdet. Cultura, skummet kultur, lettmelk, ekstra lettmelk, skummet melk, yoghurt og Kesam (1% fett) kan brukes i matlaging, til sauser og dressing.

Ost er en kilde til store mengder mettet fett. Velg lettere eller mager ost (ost med mindre enn 10 % fett) til hverdags. Ikke bruk lettere ost som pålegg på mer enn en tredel av dagens brødskiver. Vær også oppmerksom på mengde og type ost du bruker i matlagingen.

Fett kjøtt er også en kilde til store mengder mettet fett. Velg kjøtt med mindre enn 10 % fett både som middagsmat og som pålegg. Skjær bort alt synlig fett, og spis minst mulig oppblandede kjøttprodukter. Velg for eksempel karbonadedeig eller kylling-/ svinekjøttdeig fremfor kjøttdeig. Fjern skinnet på kylling, kalkun og annet fjærkre. Velg skinkeprodukter fremfor salami, fårepølse og lignende.

Spis alle typer fisk til middag flere ganger i uken. Fet fisk som makrell, sild, laks og ørret inneholder umettet fett (omega-3) og er derfor spesielt gunstig. Spis fisk som pålegg daglig. Ta i tillegg 1 skje tran, eventuelt 2 fiskeoljekapsler, daglig året rundt.

Bruk gjerne majonespålegg daglig, men i moderate mengder.
De fleste majonesprodukter inneholder mye olje og derfor mye fett (og kalorier!), men fettet er umettet og derfor gunstig.

Myk plantemargarin er en god kilde til umettet fett. Velg typer med mer enn
70 % umettet fett. Velg gjerne margarin med plantesteroler. Plantesteroler er gunstig for kolesterolet.

Bruk gjerne olje, flytende eller myk plantemargarin i matlagingen (velg typer med mer enn 70 % umettet fett). Spis mindre stekt mat. Velg heller kokt eller ovnsstekt mat, da vil behovet for fett i matlagingen reduseres.

Grove kornprodukter er viktig i hverdagskostholdet. Spis mye av alle sorter fiberrike kornprodukter. Havre er spesielt gunstig og bør brukes regelmessig. Brødet bør inneholde mer enn 6 gram fiber pr 100 g brød. Se også etter Brødskala'n på emballasjen.

Husk "5-om-dagen". Spis minst to porsjoner frukt eller bær hver dag.
Fyll halve middagstallerkenen med grønnsaker, både rå og lettkokte. Spis grønnsaker som mellommåltid, som pålegg og som pynt på pålegget. Vær raus med porsjonene.
Erter, bønner og linser kan med fordel spises ofte.

En porsjon poteter, ris eller pasta er et fint tilbehør til middagen daglig.

Bruk minst mulig sukker, sukkerholdig mat og drikke, som kjeks, kaker, is, søtt pålegg, sukkergodt, sjokolade, juice, nektar, saft og brus. Disse produktene gir ingen næringsstoffer men kan bidra til økt vekt. Sukker kan også øke triglyseridene.

Nøtter og mandler inneholder gunstig umettet fett, men er veldig kaloririke. Bruk det derfor gjerne, men i begrenset mengde. Kokosnøtten og Chillinøttene inneholder mye mettet fett og bør derfor unngås.

Kaffebønnen inneholder fettstoffer som øker kolesterolet. Velg derfor pulverkaffe (inneholder ikke fett) eller kaffe som blir filtrert. Filteret fjerner det meste av fettstoffene. Husk at kaffe tilsatt melk (for eksempel Cafe latte, cappucino) kan være en kilde til mettet fett avhengig av melketypen som brukes og mengde kaffe som drikkes.

Alkohol inneholder mye kalorier og kan derfor føre til vektøkning. Alkohol kan også øke triglyseridene.

Eggeplommen inneholder mye kolesterol. Begrens inntaket til to eggeplommer per uke. Den største kilden til kolesterol i kostholdet er likevel matvarer rike på mettet fett.

Spørreskjemaet vil ikke nødvendigvis gi et komplett bilde av ditt kosthold. Du kan få mer informasjon om kostholdet i heftet "Kostbehandling ved høye blodlipider hos voksne" (Lipidklinikken 2006).

Spørsmål 1-13 med unntak av spørsmål 10 er evaluert i forhold til veid kostholdsregistrering.

Kilde: Svilaas A, Ström EC, Svilaas T, Borgejordet Å, Thoresen M, Ose L. SmartDietTM, a health educational tool. Reproducibility and validity of a short food questionnaire for assessment of dietary habits. Nutr Metab Cardiovasc Dis 2002; 12: 60-70. Skjemaet er revidert i 2007.

64521 Wæro AS, Porsgrunn

SmartDiet™

25 spørsmål om ditt kosthold og din livsstil

Les spørsmålene og de angitte svarmulighetene nøye!

Sett kryss ved det svaret som passer best med det du *vanligvis* spiser.

Kommentarer:

Antall poeng:_____

Kostholdsvurdering	
24 poeng eller mindre:	Du bør forbedre kostholdet ditt på mange punkter, for å gjøre det mer helse- og hjertevennlig.
25-30 poeng:	Du kan forbedre kostholdet ditt på en del punkter, slik at det blir mer helse- og hjertevennlig.
31 poeng eller mer:	Du har sunne kostholdsvaner.

Navn: .....

Fødselsdato: ..... Dato for besvarelsen: .....

Navn på fastlege: .....

Adresse til fastlege: .....

1. Melk (sur/søt) og yoghurt

Hvor mange små beger med yoghurt (ca 1 dl) spiser du i løpet av en uke? Antall:.....

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

Hvilken type melk bruker du oftest som drikke, i matlagingen, på gryn, i grøt, i dessert, i kaffe/te ol.?

Helmelk • Kulturmelk • Kefir • Kaffemelk 5 % fett

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

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

Drikker/bruker mindre enn 1 liter melk i uken eller aldri

2. Fløte, rømme og lignende.

Hvilken type bruker du oftest i matlagingen, i dressing, i dip, i kaker, i kaffe/te ol.?

Kremfløte • Créme Fraiche • Seterrømme • Pisket krem

Matfløte • Lettrømme

Kaffefløte • Ekstra lettrømme • Vikingmelk • Kesam • Matyoghurt

Bruker ikke ukentlig eller bruker aldri

3. Ost på brødmaten, i matlaging, på pizza o.l.

Hvor mye ost som pålegg, regnet i osteskiver eller i spiseskjeer (for smørbar ost) spiser du daglig? Antall:.....

Til hvor mange middager per uke bruker du ost? (eks. pizza, taco, gratinering, lasagne, i saus, i salat ol.) Antall:.....

Hvilken type ost bruker du oftest?

Hvitost • Nøkkelost • Gudbrandsdalsost (G35) • Ekte geitost • Fløtemysost • Edamer • Gräddost • "Dessert oster" • Smørbare fete oster • Mozzarella • Fetaost • Revet pizza-/pastaost • Taffelost • Burgerost • Snøfrisk • Parmesan

Lettere hvitost • Lettere nøkkelost • Lettere fløtemysost • Lettere Gudbrandsdalsost • Lettere smørbare oster • Mozzarella • Fetaost • Prim med vaniljesmak

Ost med raps og solsikkeolje • Cottage cheese • Gamalost • Pultost • Mager mysost • Prim • Mager prim

Jeg bruker ost en gang i uken eller aldri

4. Kjøttpålegg

Hvilken type kjøttpålegg bruker du oftest?

Leverpostei • Salami • Lett salami • Servelat • Fårepølse • Stabburpølse • Morrpølse • Haugpølse • Reinsdyrpølse • Falukorv • Fleskepølse • Sylte • Lammerull • Paté • Fenalår

Kokt/røkt skinke • Hamburgerrygg • Krydderskinke Pastramiskinke • Roastbiff • Bankekjøtt • Kylling- og kalkunpålegg • Lett servelat • Kalverull • Spekeskinke uten fettrand • oljebaserte posteier (Vita/Mills, Delikat, Gilde) eller mager leverpostei

Bruker ikke kjøttpålegg ukentlig eller bruker aldri

5. Kjøtt til middag

Hvilken type bruker du oftest?

Familiedeig • Medisterdeig • Grillpølse • Wienerpølse • Kjøttpølse • Medisterpølse • Knakkpølse • Nakkekoteletter med fettrand • Lammekoteletter • Medisterkake • Wienerschnitzel • Bacon • Flesk • Grillben • Fårekjøtt

Kjøttdeig (okse, lam) • Kyllingpølse • Lettpølse • Kjøpte karbonader • Hamburger • Kebabkjøtt • Kjøttkaker • Kjøttpudding • Kamkoteletter med fettrand • Nakkekoteletter uten fettrand • Kylling, kalkun og høne med skinn • Bayonneskinke med fettrand • Hamburgerrygg med fettrand

Karbonadedeig • Kjøttdeig (svin, kylling) • Biff • Filet (kylling, svin, okse, lam) • Viltkjøtt • Stek uten fettrand • Bogskinke • Kamkoteletter uten fettrand • Kjøtt uten synlig fett • Kylling, kalkun og høne uten skinn

Jeg spiser ikke kjøtt ukentlig eller aldri

6. Fiskepålegg

Hvor ofte har du fiskepålegg på brødmaten?

Eksempler: Laks • Makrell • Sild • Sardiner • Brisling • Tunfisk • Reker • Krabbe • Crab-sticks • Fiskepudding • Fiskekaker m.fl

På inntil 1 brødskive i uken, eller aldri

På 2-4 brødskiver i uken

På 5 eller flere brødskiver per uke

7. Fisk til middag

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

Inntil en gang i uken eller aldri

2 ganger i uken

3 eller flere ganger i uken

Til hvor mange av disse middagene spiser du fet fisk ukentlig?

Antall:.....

Med fet fisk menes f.eks. ørret, laks, makrell, kveite, sild.

8. Majones, remulade og kaviar

Hvor ofte bruker du majonesprodukter, remulade og/eller kaviar på brødmaten?

Eksempler: Majones • Rekesalat • Italiensk salat • Crab-stick salat • Skagensalat • Frokostsalat • Remulade • Kaviar/kaviarmix mfl.

På inntil 1 brødskive i uken, eller aldri

På 2-7 brødskiver i uken

På 8 eller flere brødskiver per uke

9. Smør eller margarin på brødmaten

Hvilken type bruker du oftest?

Alle typer smør • Smøregod • Bremyk • Brelett • Melange margarin • Per margarin • Soft margarin uten salt og melk • Letta

Soft Flora • Soft Light • Soya margarin • Soya lett margarin • Oliven margarin • Olivero • Solsikke margarin • Soft Ekstra

Vita • Vita lett • Vita Pro-aktiv • Becel Pro-activ • Münsterland Organic Margarin

Bruker vanligvis ikke smør eller margarin på brødmaten

10. Bruker du et produkt som inneholder plantesteroler?

Bruker du produkter som inneholder plantesteroler?

Eksempler: Vita pro-aktiv • Becel pro-aktiv • yoghurt shot ◯ ja ◯ nei

11. Fett i matlagingen

Hvilken type fett bruker du oftest til steking, baking, i saus, som dressing ol.?

Alle typer smør • Bremyk • Smøregod • Melange margarin • Per margarin • Soft Flora stekemargarin • Soya stekemargarin

Soft Flora • Soya margarin • Solsikke margarin • Oliven margarin • Olivero • Soft Ekstra

Olje • Flytende margarin • Vita

Bruker vanligvis ikke fett i matlagingen

12. Brød, knekkebrød og andre kornprodukter

Hvor mange skiver brød, rundstykker eller knekkebrød spiser du daglig? Antall:.....

Hvor mange porsjoner havregrøt, kornblanding eller andre typer frokost-blandinger spiser du daglig? Antall:.....

Hvor grove kornvarer bruker du?

Spiser oftest brød, knekkebrød, kornblandinger og lignende med lite fiber, dvs fint mel er hovedingrediensen og matvaren har mindre enn 50 % grovhet.
Eksempler: Kneippbrød • Loff • Fine rundstykker • Baguetter • Ciabatta • Lyst knekkebrød • Riskaker • Puffet ris • Cornflakes • Havrenøtter • Frokostkorn med (sjokolade, honning, sukker) m.fl.

Spiser oftest brød, knekkebrød, kornblandinger og lignende med mye fiber, dvs sammalt mel er hovedingrediens og matvaren har mer enn 50 % grovhet.
Eksempler: Rugbrød • Pumpernikkel • Mørke knekkebrød • Rugsprø • Fiberrik • Havregryn • Weetabix, Havrefras • Shredded wheat m.fl.

Spiser ikke brød, knekkebrød, eller andre kornprodukter

13. Grønnsaker, frukt og bær

Hvor mange porsjoner grønnsaker, frukt og bær spiser du daglig?

1 porsjon=150g som tilsvarer ca 2 gulrøtter eller ca 1 1/2 eple

Mindre enn 2 porsjoner (< 300g)

2-4 porsjoner (300-600g)

4 porsjoner eller mer (≥ 600g)

Hvor mange av disse porsjonene er grønnsaker? Antall:.....

Totalt antall poeng: ____

14. Belgvekster

Spiser du belgvekster ukentlig? ◯ Ja ◯ Nei

Eksempel: hvite tomatbønner, brune bønner, kikerter, linser, erter, sukkererter.

15. Potet, ris og pasta

Hvor mange porsjoner poteter, ris og/eller pasta spiser du daglig?

En porsjon tilsvarer 2 poteter eller 1 dl kokt ris eller 1 dl kokt pasta/spagetti

◯ Spiser ikke ◯ 0-1 porsjon ◯ 2 porsjoner ◯ 3 porsjoner eller fler

16. Sukker, søtt pålegg, søt drikke, kaker, kjeks og annet snacks

Bruker du mer enn 1,5 dl søt drikke daglig? ◯ Ja ◯ Nei

Eksempel: Saft • Brus • Fruktjuice • Nektar

Spiser du sjokolade ukentlig? ◯ Ja ◯ Nei

Spiser du fløteis ukentlig? ◯ Ja ◯ Nei

Spiser du annet snacks som potetgull, ostepop, baconcrisp, tortilla chips o.l. ukentlig? ◯ Ja ◯ Nei

Spiser du kake eller kjeks ukentlig? ◯ Ja ◯ Nei

Spiser du smågodt, seigmenn eller annet sukkergodt ukentlig? ◯ Ja ◯ Nei

17. Nøtter og mandler

Spiser du nøtter/mandler ukentlig? ◯ Ja ◯ Nei

18. Kaffe

Drikker du kaffe? ◯ Ja ◯ Nei

Hvis ja, hvilken type?:.....

F.eks. cappucino, café latte, kokekaffe, traktekaffe, pulverkaffe

19. Alkohol

Drikker du alkohol? ◯ Ja ◯ Nei

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

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

1 enhet =
1 glass vin (125 ml)
1 glass øl (0.33 l)
4 cl brennevin

20. Egg

Hvor mange egg, inkludert i matlaging, spiser du per uke? Antall.....

1. Måltidsmønster

Hvor mange måltider spiser du daglig? ◯ 1 til 2 måltider ◯ 3 måltider ◯ 4 måltider ◯ 5 eller flere måltider

2. Høyde og vekt

Høyde:..... cm Vekt:..... kg

Jeg ønsker å gå ned i vekt ◯ Nei ◯ Ja

Hvis ja, hvor mange kilo ønsker du å gå ned i vekt? ..... kg

3. Røyk/snus

Røyker du? ◯ Nei ◯ Ja ◯ Ja, selskapsrøyker

Hvis ja, hvor mange sigaretter/piper røyker du per dag? Antall .....

Snuser du? ◯ Nei ◯ Ja

Hvis ja, hvor mange porsjoner snuser du per dag? Antall .....

4. Mosjon

Hvor ofte mosjonerer du i minst 30 minutter?

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

◯ Sjeldnere enn 1 gang per uke eller aldri

◯ 1 til 2 ganger per uke ◯ 3 eller flere ganger per uke

5. Kosttilskudd

Bruker du kosttilskudd? ◯ Nei ◯ Tran ◯ Fiskeoljekapsler/omega3-kapsler

◯ Multivitaminpreparat ◯ Annet:.....

De gode rådene finner du her

Mettet fett er kolesterøløkende. Reduser derfor inntaket av matvarer med mye mettet fett. Velg i stedet matvarer med mye umettet fett som kan senke kolesterolet.

Drikk mager melk, 1/2 liter skummet, søt eller sur, daglig. Dersom du ikke drikker melk daglig, kan det føre til et for lavt inntak av kalsium.

Alle fløte- og rømmetyper inneholder mye mettet fett og anbefales ikke i hverdagskostholdet. Cultura, skummet kultur, lettmelk, ekstra lettmelk, skummet melk, yoghurt og Kesam (1% fett) kan brukes i matlaging, til sauser og dressing.

Ost er en kilde til store mengder mettet fett. Velg lettere eller mager ost (ost med mindre enn 10 % fett) til hverdags. Ikke bruk lettere ost som pålegg på mer enn en tredel av dagens brødskiver. Vær også oppmerksom på mengde og type ost du bruker i matlagingen.

Fett kjøtt er også en kilde til store mengder mettet fett. Velg kjøtt med mindre enn 10 % fett både som middagsmat og som pålegg. Skjær bort alt synlig fett, og spis minst mulig oppblandede kjøttprodukter. Velg for eksempel karbonadedeig eller kylling-/ svinekjøttdeig fremfor kjøttdeig. Fjern skinnet på kylling, kalkun og annet fjærkre. Velg skinkeprodukter fremfor salami, fårepølse og lignende.

Spis alle typer fisk til middag flere ganger i uken. Fet fisk som makrell, sild, laks og ørret inneholder umettet fett (omega-3) og er derfor spesielt gunstig. Spis fisk som pålegg daglig. Ta i tillegg 1 skje tran, eventuelt 2 fiskeoljekapsler, daglig året rundt.

Bruk gjerne majonespålegg daglig, men i moderate mengder.
De fleste majonesprodukter inneholder mye olje og derfor mye fett (og kalorier!), men fettet er umettet og derfor gunstig.

Myk plantemargarin er en god kilde til umettet fett. Velg typer med mer enn
70 % umettet fett. Velg gjerne margarin med plantesteroler. Plantesteroler er gunstig for kolesterolet.

Bruk gjerne olje, flytende eller myk plantemargarin i matlagingen (velg typer med mer enn 70 % umettet fett). Spis mindre stekt mat. Velg heller kokt eller ovnsstekt mat, da vil behovet for fett i matlagingen reduseres.

Grove kornprodukter er viktig i hverdagskostholdet. Spis mye av alle sorter fiberrike kornprodukter. Havre er spesielt gunstig og bør brukes regelmessig. Brødet bør inneholde mer enn 6 gram fiber pr 100 g brød. Se også etter Brødskala'n på emballasjen.

Husk "5-om-dagen". Spis minst to porsjoner frukt eller bær hver dag.
Fyll halve middagstallerkenen med grønnsaker, både rå og lettkokte. Spis grønnsaker som mellommåltid, som pålegg og som pynt på pålegget. Vær raus med porsjonene.
Erter, bønner og linser kan med fordel spises ofte.

En porsjon poteter, ris eller pasta er et fint tilbehør til middagen daglig.

Bruk minst mulig sukker, sukkerholdig mat og drikke, som kjeks, kaker, is, søtt pålegg, sukkergodt, sjokolade, juice, nektar, saft og brus. Disse produktene gir ingen næringsstoffer men kan bidra til økt vekt. Sukker kan også øke triglyseridene.

Nøtter og mandler inneholder gunstig umettet fett, men er veldig kaloririke. Bruk det derfor gjerne, men i begrenset mengde. Kokosnøtten og Chillinøttene inneholder mye mettet fett og bør derfor unngås.

Kaffebønnen inneholder fettstoffer som øker kolesterolet. Velg derfor pulverkaffe (inneholder ikke fett) eller kaffe som blir filtrert. Filteret fjerner det meste av fettstoffene. Husk at kaffe tilsatt melk (for eksempel Cafe latte, cappucino) kan være en kilde til mettet fett avhengig av melketypen som brukes og mengde kaffe som drikkes.

Alkohol inneholder mye kalorier og kan derfor føre til vektøkning. Alkohol kan også øke triglyseridene.

Eggeplommen inneholder mye kolesterol. Begrens inntaket til to eggeplommer per uke. Den største kilden til kolesterol i kostholdet er likevel matvarer rike på mettet fett.

Spørreskjemaet vil ikke nødvendigvis gi et komplett bilde av ditt kosthold. Du kan få mer informasjon om kostholdet i heftet "Kostbehandling ved høye blodlipider hos voksne" (Lipidklinikken 2006).

Spørsmål 1-13 med unntak av spørsmål 10 er evaluert i forhold til veid kostholdsregistrering.

Kilde: Svilaas A, Ström EC, Svilaas T, Borgejordet Å, Thoresen M, Ose L. SmartDietTM, a health educational tool. Reproducibility and validity of a short food questionnaire for assessment of dietary habits. Nutr Metab Cardiovasc Dis 2002; 12: 60-70. Skjemaet er revidert i 2007.

64521 Wæro AS. Porsgrunn

SmartDiet™

25 spørsmål om ditt kosthold og din livsstil

Les spørsmålene og de angitte svarmulighetene nøye!

Sett kryss ved det svaret som passer best med det du *vanligvis* spiser.

Kommentarer:

Antall poeng:_____

Kostholdsvurdering	
24 poeng eller mindre:	Du bør forbedre kostholdet ditt på mange punkter, for å gjøre det mer helse- og hjertevennlig.
25-30 poeng:	Du kan forbedre kostholdet ditt på en del punkter, slik at det blir mer helse- og hjertevennlig.
31 poeng eller mer:	Du har sunne kostholdsvaner.

Navn: .....

Fødselsdato: ..... Dato for besvarelsen: .....

Navn på fastlege: .....

Adresse til fastlege: .....

1. Melk (sur/søt) og yoghurt

Hvor mange små beger med yoghurt (ca 1 dl) spiser du i løpet av en uke? Antall:.....

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

Hvilken type melk bruker du oftest som drikke, i matlagingen, på gryn, i grøt, i dessert, i kaffe/te ol.?

Helmelk • Kulturmelk • Kefir • Kaffemelk 5 % fett

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

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

Drikker/bruker mindre enn 1 liter melk i uken eller aldri

2. Fløte, rømme og lignende.

Hvilken type bruker du oftest i matlagingen, i dressing, i dip, i kaker, i kaffe/te ol.?

Kremfløte • Créme Fraiche • Seterrømme • Pisket krem

Matfløte • Lettrømme

Kaffefløte • Ekstra lettrømme • Vikingmelk • Kesam • Matyoghurt

Bruker ikke ukentlig eller bruker aldri

3. Ost på brødmaten, i matlaging, på pizza o.l.

Hvor mye ost som pålegg, regnet i osteskiver eller i spiseskjeer (for smørbar ost) spiser du daglig? Antall:.....

Til hvor mange middager per uke bruker du ost? (eks. pizza, taco, gratinering, lasagne, i saus, i salat ol.) Antall:.....

Hvilken type ost bruker du oftest?

Hvitost • Nøkkelost • Gudbrandsdalsost (G35) • Ekte geitost • Fløtemysost • Edamer • Gräddost • "Dessert oster" • Smørbare fete oster • Mozzarella • Fetaost • Revet pizza-/pastaost • Taffelost • Burgerost • Snøfrisk • Parmesan

Lettere hvitost • Lettere nøkkelost • Lettere fløtemysost • Lettere Gudbrandsdalsost • Lettere smørbare oster • Mozzarella • Fetaost • Prim med vaniljesmak

Ost med raps og solsikkeolje • Cottage cheese • Gamalost • Pultost • Mager mysost • Prim • Mager prim

Jeg bruker ost en gang i uken eller aldri

4. Kjøttpålegg

Hvilken type kjøttpålegg bruker du oftest?

Leverpostei • Salami • Lett salami • Servelat • Fårepølse • Stabburpølse • Morrpølse • Haugpølse • Reinsdyrpølse • Falukorv • Fleskepølse • Sylte • Lammerull • Paté • Fenalår

Kokt/røkt skinke • Hamburgerrygg • Krydderskinke Pastramiskinke • Roastbiff • Bankekjøtt • Kylling- og kalkunpålegg • Lett servelat • Kalverull • Spekeskinke uten fettrand • oljebaserte posteier (Vita/Mills, Delikat, Gilde) eller mager leverpostei

Bruker ikke kjøttpålegg ukentlig eller bruker aldri

5. Kjøtt til middag

Hvilken type bruker du oftest?

Familiedeig • Medisterdeig • Grillpølse • Wienerpølse • Kjøttpølse • Medisterpølse • Knakkpølse • Nakkekoteletter med fettrand • Lammekoteletter • Medisterkake • Wienerschnitzel • Bacon • Flesk • Grillben • Fårekjøtt

Kjøttdeig (okse, lam) • Kyllingpølse • Lettpølse • Kjøpte karbonader • Hamburger • Kebabkjøtt • Kjøttkaker • Kjøttpudding • Kamkoteletter med fettrand • Nakkekoteletter uten fettrand • Kylling, kalkun og høne med skinn • Bayonneskinke med fettrand • Hamburgerrygg med fettrand

Karbonadedeig • Kjøttdeig (svin, kylling) • Biff • Filet (kylling, svin, okse, lam) • Viltkjøtt • Stek uten fettrand • Bogskinke • Kamkoteletter uten fettrand • Kjøtt uten synlig fett • Kylling, kalkun og høne uten skinn

Jeg spiser ikke kjøtt ukentlig eller aldri

6. Fiskepålegg

Hvor ofte har du fiskepålegg på brødmaten?

Eksempler: Laks • Makrell • Sild • Sardiner • Brisling • Tunfisk • Reker • Krabbe • Crab-sticks • Fiskepudding • Fiskekaker m.fl

På inntil 1 brødskive i uken, eller aldri

På 2-4 brødskiver i uken

På 5 eller flere brødskiver per uke

7. Fisk til middag

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

Inntil en gang i uken eller aldri

2 ganger i uken

3 eller flere ganger i uken

Til hvor mange av disse middagene spiser du fet fisk ukentlig?

Antall:.....

Med fet fisk menes f.eks. ørret, laks, makrell, kveite, sild.

8. Majones, remulade og kaviar

Hvor ofte bruker du majonesprodukter, remulade og/eller kaviar på brødmaten?

Eksempler: Majones • Rekesalat • Italiensk salat • Crab-stick salat • Skagensalat • Frokostsalat • Remulade • Kaviar/kaviarmix mfl.

På inntil 1 brødskive i uken, eller aldri

På 2-7 brødskiver i uken

På 8 eller flere brødskiver per uke

9. Smør eller margarin på brødmaten

Hvilken type bruker du oftest?

Alle typer smør • Smøregod • Bremyk • Brelett • Melange margarin • Per margarin • Soft margarin uten salt og melk • Letta

Soft Flora • Soft Light • Soya margarin • Soya lett margarin • Oliven margarin • Olivero • Solsikke margarin • Soft Ekstra

Vita • Vita lett • Vita Pro-aktiv • Becel Pro-activ • Münsterland Organic Margarin

Bruker vanligvis ikke smør eller margarin på brødmaten

10. Bruker du et produkt som inneholder plantesteroler?

Bruker du produkter som inneholder plantesteroler?

Eksempler: Vita pro-aktiv • Becel pro-aktiv • yoghurt shot ◯ ja ◯ nei

11. Fett i matlagingen

Hvilken type fett bruker du oftest til steking, baking, i saus, som dressing ol.?

Alle typer smør • Bremyk • Smøregod • Melange margarin • Per margarin • Soft Flora stekemargarin • Soya stekemargarin

Soft Flora • Soya margarin • Solsikke margarin • Oliven margarin • Olivero • Soft Ekstra

Olje • Flytende margarin • Vita

Bruker vanligvis ikke fett i matlagingen

12. Brød, knekkebrød og andre kornprodukter

Hvor mange skiver brød, rundstykker eller knekkebrød spiser du daglig? Antall:.....

Hvor mange porsjoner havregrøt, kornblanding eller andre typer frokost-blandinger spiser du daglig? Antall:.....

Hvor grove kornvarer bruker du?

Spiser oftest brød, knekkebrød, kornblandinger og lignende med lite fiber, dvs fint mel er hovedingrediensen og matvaren har mindre enn 50 % grovhet.
Eksempler: Kneippbrød • Loff • Fine rundstykker • Baguetter • Ciabatta • Lyst knekkebrød • Riskaker • Puffet ris • Cornflakes • Havrenøtter • Frokostkorn med (sjokolade, honning, sukker) m.fl.

Spiser oftest brød, knekkebrød, kornblandinger og lignende med mye fiber, dvs sammalt mel er hovedingrediens og matvaren har mer enn 50 % grovhet.
Eksempler: Rugbrød • Pumpernikkel • Mørke knekkebrød • Rugsprø • Fiberrik • Havregryn • Weetabix, Havrefras • Shredded wheat m.fl.

Spiser ikke brød, knekkebrød, eller andre kornprodukter

13. Grønnsaker, frukt og bær

Hvor mange porsjoner grønnsaker, frukt og bær spiser du daglig?

1 porsjon=150g som tilsvarer ca 2 gulrøtter eller ca 1 1/2 eple

Mindre enn 2 porsjoner (< 300g)

2-4 porsjoner (300-600g)

4 porsjoner eller mer (≥ 600g)

Hvor mange av disse porsjonene er grønnsaker? Antall:.....

Totalt antall poeng: ____

14. Belgvekster

Spiser du belgvekster ukentlig? ◯ Ja ◯ Nei

Eksempel: hvite tomatbønner, brune bønner, kikerter, linser, erter, sukkererter.

15. Potet, ris og pasta

Hvor mange porsjoner poteter, ris og/eller pasta spiser du daglig?

En porsjon tilsvarer 2 poteter eller 1 dl kokt ris eller 1 dl kokt pasta/spagetti

◯ Spiser ikke ◯ 0-1 porsjon ◯ 2 porsjoner ◯ 3 porsjoner eller fler

16. Sukker, søtt pålegg, søt drikke, kaker, kjeks og annet snacks

Bruker du mer enn 1,5 dl søt drikke daglig? ◯ Ja ◯ Nei

Eksempel: Saft • Brus • Fruktjuice • Nektar

Spiser du sjokolade ukentlig? ◯ Ja ◯ Nei

Spiser du fløteis ukentlig? ◯ Ja ◯ Nei

Spiser du annet snacks som potetgull, ostepop, baconcrisp, tortilla chips o.l. ukentlig? ◯ Ja ◯ Nei

Spiser du kake eller kjeks ukentlig? ◯ Ja ◯ Nei

Spiser du smågodt, seigmenn eller annet sukkergodt ukentlig? ◯ Ja ◯ Nei

17. Nøtter og mandler

Spiser du nøtter/mandler ukentlig? ◯ Ja ◯ Nei

18. Kaffe

Drikker du kaffe? ◯ Ja ◯ Nei

Hvis ja, hvilken type?:.....

F.eks. cappucino, café latte, kokekaffe, traktekaffe, pulverkaffe

19. Alkohol

Drikker du alkohol? ◯ Ja ◯ Nei

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

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

1 enhet =
1 glass vin (125 ml)
1 glass øl (0.33 l)
4 cl brennevin

20. Egg

Hvor mange egg, inkludert i matlaging, spiser du per uke? Antall.....

1. Måltidsmønster

Hvor mange måltider spiser du daglig? ◯ 1 til 2 måltider ◯ 3 måltider ◯ 4 måltider ◯ 5 eller flere måltider

2. Høyde og vekt

Høyde:..... cm Vekt:..... kg

Jeg ønsker å gå ned i vekt ◯ Nei ◯ Ja

Hvis ja, hvor mange kilo ønsker du å gå ned i vekt? ..... kg

3. Røyk/snus

Røyker du? ◯ Nei ◯ Ja ◯ Ja, selskapsrøyker

Hvis ja, hvor mange sigaretter/piper røyker du per dag? Antall .....

Snuser du? ◯ Nei ◯ Ja

Hvis ja, hvor mange porsjoner snuser du per dag? Antall .....

4. Mosjon

Hvor ofte mosjonerer du i minst 30 minutter?

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

◯ Sjeldnere enn 1 gang per uke eller aldri

◯ 1 til 2 ganger per uke ◯ 3 eller flere ganger per uke

5. Kosttilskudd

Bruker du kosttilskudd? ◯ Nei ◯ Tran ◯ Fiskeoljekapsler/omega3-kapsler

◯ Multivitaminpreparat ◯ Annet:.....

Appendix 4. Patient's preference form.

ID kode:

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.

Dato.....

1. Hvor får du hovedoppfølgingen av din FH?

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

2. Hvor ofte er du hos fastlegen?

Antall ganger per år: _____

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

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

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

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

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

1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Svært misfornøyd									Svært fornøyd

økende fornøydhet →

Hva synes du følgende utsagn:

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

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

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

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

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

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

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

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

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

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

Hjertelig takk for innsatsen!

Forespørsel om deltakelse i forskningsprosjektet

”Treat To Target Familiær Hyperkolsterolemi”

Bakgrunn og hensikt

Ved dette spør vi deg om å delta i oppfølgingen av forsknings- og kvalitetssikringsstudien som du deltok i årene 2006-07, Treat To Target – FH studien. Man foretar nå en 8-9 års oppfølging, for å se hvordan det har gått disse årene både vedrørende intensivert behandling, lipidverdier, bivirkninger, risiko og hjertekarhendelser. Man undersøker også effekten av livsstilsendringene.

Hva innebærer studien?

Studien innebærer at du møter ved Lipidklinikken, eller at du deltar ved et telefonintervju. Konsultasjonen ved Lipidklinikken vil fungere som en vanlig lege- og klinisk ernæringsfysiolog kontroll.
Hvis du ønsker telefonintervju, vil bli spurt om ”de vanlige journalopplysningene” som blant annet vekt, høyde, blodtrykk, lipidverdier, allergier, kosthold, sykdommer i denne perioden, medikamentbruk og eventuelle bivirkninger av dem. Du vil også bli spurt om å fylle ut SmartDiet, som du kjenner til, og vil få tilbud om en egen samtale med en trenet student i klinisk ernæringsvitenskap.
Dersom det er mer enn 6 måneder siden du sist målte lipidverdiene, eller dersom du har endret behandlingsopplegget siden forrige blodprøve, eller dersom tidligere prøver ikke inneholder alle blodprøvesvarene vi ser etter, vil du bli spurt om å avgi en ny blodprøve.

Fordeler og ulemper

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

Hva skjer med prøvene og informasjonen om deg?

Informasjonen som registreres om deg, vil bli sammenfattet i et vanlig klinisk journalnotat, og sendt til deg selv og dine leger, slik som alltid tidligere fra overlege Kjell Erik Arnesen. Data vil også bli registrert i en database, og bruk til forskning og forbedring av våre tiltak og rutiner.
Forskningsopplysningene og prøvesvarene vil bli behandlet uten navn og fødselsnummer, eller andre

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

Frivillig deltakelse

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

Dersom du ønsker å delta, må du undertegne samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg, eller har spørsmål til studien, så kontakt overlege Kjell-Erik Arnesen på telefon 2307 5613 eller mobil 924 85 970.

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

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

Samtykkeerklæring følger etter kapittel B.

Kapittel A- utdypende forklaring av hva studien innebærer

Kriterier for deltakelse

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

Bakgrunnsinformasjon om studien

Familiær hyperkolesterolemi (FH) er en arvelig tilstand hvor en genendring fører til redusert antall LDL-reseptorer. Det fører til et høyt kolesterol i hele livet. Tidlig og livslang kolesterolsenkende behandling sammen med optimal og risikolav livsstil, forhindrer i betydelig grad åreforkalkninger. Man oppnår nærmest like god livsprognose som normalbefolkningen. Vi ønsker nå å etterundersøke deltakerne, for å bedømme effektene over en 8-9 års periode.

Undersøkelser, blodprøver og annet den inkluderte må gjennom

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

Tidsskjema – hva skjer og når skjer det?

Konsultasjonen og intervjuene vil bli startet i løpet av slutten av 2015 og våren 2016.

Kapittel B - Personvern, økonomi og forsikring

Personvern

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

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

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

Økonomi

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

Forsikring

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

Informasjon om utfallet av studien

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

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

(Navn med blokkbokstaver)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

(Navn med blokkbokstaver)

Appendix 6. Approval by the Regional Ethical Committee for Medical Research

REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anette Solli Karlsen	22845522	18.11.2015	2014/753/REK sør-øst A
			Deres dato:	**Deres referanse:**
			02.11.2015	

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 prosjektendring datert 02.11.2015 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:
-Nye medarbeidere. Student Irene Mork og Professor Kjetil Retterstøl knyttes til prosjektet som medarbeidere.
-Ny sluttdato. Prosjektet søkes forlenget til 31.12.2016.
-Økning i antall forskningsdeltakere. Prosjektet søkes utvidet til å omfatte oppfølging av ytterligere 265 pasienter, deltakere i tidligere studie TTT-FH Kvalitetssikringsprosjekt.

Komiteens leder har vurdert søknaden og har ingen innvendinger til de endringer som er beskrevet.

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

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*