Treat-To-Target
Familial Hypercholesterolemia

A prospective study in patients with Familial Hypercholesterolemia – Achievements after long intensive lipid lowering treatment in a specialized Lipid Clinic.

Master thesis by Karoline Randsborg
Department of Nutrition, Faculty of Medicine
University of Oslo
November 2017
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Supervisors: Kjell-Erik Arnesen and Kjetil Retterstøl

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http://www.duo.uio.no

Trykk: Retrosportalen, Universiteten i Oslo.
Summary

**Background and aim:** Familial hypercholesterolemia (FH) is an autosomal dominant genetic disease, characterized by severely elevated LDL-cholesterol (LDL-C) from birth. This accelerates the atherosclerotic process and causes premature cardiovascular disease (CVD). Early detection and initiation of lipid lowering medications (LLM), together with a healthy diet and lifestyle, is essential to reduce the risk of premature CVD. The aim of this thesis is to describe what is achievable with an intensive treatment in a specialized Lipid Clinic, with an especial focus of the prospective period of eight to ten years. Especially, we focus on describing the age at diagnosis and the start of LLM, the blood lipids and blood glucose, anthropometry, diet and lifestyle. Finally, the thesis is concluded with an investigation of the differences between the patients with and without CVD regarding to the mentioned factors.

**Subjects and method:** The study started in 2006 with 357 adult heterozygous FH patients attending visit 1 (V1). 332 of them attended V2 during 2007, and 216 patients attended V3, this included 10 patients who missed V2. V3 was conducted in three parts during the fall 2014, spring 2016 and spring 2017. Data on medical treatment, diet and lifestyle and patients preference about the treatment were collected on all visits through ordinary medical examinations, the patient’s medical records and Smart Diet forms. The thesis describes first the status at V3, secondly the changes during the study, and then a comparison of the patients with and without CVD at V3.

**Results:** Mean (95% CI) known first measured total cholesterol (TC) was at age 26.8 years (25.0, 28.5), and the start with LLM was at 31.9 years (29.8, 34.0) for men and 37.8 years (35.6, 39.9) for women. Over 90% used statin treatment, the vast majority used high intensity at V3. Mean (95% CI) TC and LDL-C on V3 was 5.0 mmol/L (4.8, 5.2) and 3.0 mmol/L (2.9, 3.2), respectively. This was over 50% reduction from untreated levels. 30.3% and 8.5% for the patients in primary and secondary prevention, respectively, achieved treatment targets at V3. Apolipoprotein B and A1, triglycerides and glucose blood values increased significantly (p<0.05) during the study. The weight and waist circumference increased during the study, and close too one out of three had metabolic syndrome at V3. Smart Diet score mean (95% CI) was 36.2 points (35.7, 36.7) of a maximum 45 points, a significant increase during the study. During the study the number of smokers reduced 30%, but only approximately 50% of the patients had a physical activity level according to the Norwegian recommendations.
throughout the study. 29.1% had CVD at V3, and they were on average 10 years older in every scenario: at first measured TC, at the first visit to the Lipid Clinic, and when they started with LLM. Further the patients with CVD had a higher Smart Diet score, and the men had a higher occurrence of metabolic syndrome compared to patients without CVD.

**Conclusion:** The average FH patient in this population was diagnosed relatively late in life, and subsequently started LLM late, and those with CVD even later than those without. Even with intensive LLM few reached LDL-treatment targets set by European Society of Atherosclerosis, but in average a reduction over 50% from untreated TC and LDL-C levels were achieved by V3. A worrisome high percentage developed towards a metabolic syndrome. Even though the diet became more cardio protective and 30% of the smokers quit smoking during the study, the physical activity level continued to be low and the weight increased. This highlights, yet again previous findings, that early diagnosis and treatment is essential. Also a cardio-protective diet with a well balanced energy intake, the use of mon- and polyunsaturated fat instead of saturated fat, and low consumption of sugar and salt, should constantly be put in focus together with the importance of doing daily physical activity and stop smoking.
Acknowledgements

The present work has been conducted from January 2017 to November 2017 at the Lipid Clinic, Rikshospitalet, Oslo University Hospital and at the Department of Nutrition, Faculty of Medicine, University of Oslo.

First of all, I would like to thank my supervisors Kjell-Erik Arnesen and Kjetil Retterstøl. Kjell-Erik you have been so positive, supporting and encouraging during the data collecting and help in the writing process, and you have also let me be involved in the working environment at the Lipid Clinic. Kjetil, you have given me good advice and guidance, and you make me see things from new angles. This has been especially important during the writing process. You are both experts in the field and you have passion for you work. I have appreciated having you as my supervisors. Thanks for everything you have taught me!

Further, a special thanks to Malene Thorvall and Irene Mork, for having laid the basis for this thesis and done a fantastic job with the data material before me. Irene, thank you for being so kind and helpful with all my questions during the whole process.

Last but not least, I am very thankful to my classmates for sharing frustrations, and for good discussions especially over the last year. Five years with coffee-brakes, lunches and celebrations of achievements have been a blast!!

Oslo, November 2017
Karoline Randsborg
TABLE OF CONTENTS

1 Introduction ........................................................................................................................................ 16

1.1 Cardiovascular disease .............................................................................................................. 16
1.2 Lipoprotein metabolism .............................................................................................................. 16
1.3 The atherosclerosis process ....................................................................................................... 17
1.4 Familial hypercholesterolemia ..................................................................................................... 18
  1.4.1 Genetics and pathophysiology ............................................................................................. 19
  1.4.2 Prevalence .......................................................................................................................... 19
  1.4.3 Diagnosis and clinical presentation ...................................................................................... 20
  1.4.4 Risk factors for cardiovascular disease .............................................................................. 20
  1.4.5 Treatment .......................................................................................................................... 28
1.5 Gaps in the knowledge of FH ...................................................................................................... 32

2 Aim of the study ................................................................................................................................ 33

2.1 Thesis rationale .......................................................................................................................... 33
2.2 Thesis objectives ........................................................................................................................ 33
2.3 Hypothesis ..................................................................................................................................... 34

3 Subjects and methods ...................................................................................................................... 35

3.1 Recruitment of participants ........................................................................................................ 35
  3.1.1 Enrolment and the first visit ............................................................................................... 35
  3.1.2 The second visit ................................................................................................................ 35
  3.1.3 The third visit .................................................................................................................... 35
3.2 Materials ....................................................................................................................................... 38
  3.2.1 Collection of data ............................................................................................................... 38
  3.2.2 Statistical methods ........................................................................................................... 45

4 Results .............................................................................................................................................. 47

4.1 Description of the FH population at V3 .................................................................................... 47
  4.1.1 Clinical characterization ...................................................................................................... 47
  4.1.2 Lipid lowering medication .................................................................................................. 48
  4.1.3 Adverse effects .................................................................................................................. 50
  4.1.4 Patients without statin therapy and/or lipid lowering medication .................................... 51
  4.1.5 Blood parameters .............................................................................................................. 52
  4.1.6 Achievement of LDL-C treatment goal ............................................................................ 53
  4.1.7 Dietary and lifestyle factors ............................................................................................... 54
4.2 Changes in cardiovascular risk factors ...................................................................................... 56
  4.2.1 Anthropometric data ........................................................................................................ 56
  4.2.2 Blood parameters .............................................................................................................. 56
  4.2.3 Dietary and lifestyle factors ............................................................................................... 58
  4.2.4 Patients belief and preferences about lifestyle and treatment ........................................ 60
4.3 Comparison between those with and without CVD .............................................................. 61
  4.3.1 Clinical characterization, anthropometry and metabolic syndrome. ............................... 61
  4.3.2 Lipid lowering medications .............................................................................................. 62
  4.3.3 Blood parameters .............................................................................................................. 63
  4.3.4 Dietary factors .................................................................................................................. 64
  4.3.5 Lifestyle factors ................................................................................................................ 65
4.4 Cardiovascular events and death .............................................................................................. 66
5 Discussion ............................................................................................................. 67
5.1 Subjects and methods ...................................................................................... 67
  5.1.1 Participants ................................................................................................ 67
  5.1.2 Study design and implementation of the study ........................................ 69
  5.1.3 Data processing ....................................................................................... 70
5.2 Results ............................................................................................................. 72
  5.2.1 Present state at V3 and the changes over eight to ten years ................. 72
  5.2.2 Comparison between those with and without CVD at V3 ................... 85

6 Conclusion ....................................................................................................... 89

7 Clinical implications and future perspectives .................................................. 91

8 Conflicts of interest .......................................................................................... 92

Reference ........................................................................................................... 93

Appendices ......................................................................................................... 104
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>AP</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>APO</td>
<td>Apolipoprotein</td>
</tr>
<tr>
<td>APO A1</td>
<td>Apolipoprotein A1</td>
</tr>
<tr>
<td>APO B</td>
<td>Apolipoprotein B</td>
</tr>
<tr>
<td>AMORIS</td>
<td>The Apolipoprotein Related Mortality Risk study</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
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<tr>
<td>CASCADE</td>
<td>Cascade Screening for Awareness and Detection</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CM</td>
<td>Chylomicrons</td>
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<tr>
<td>cm</td>
<td>Centimetre</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DALY</td>
<td>Disability-adjusted life years</td>
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<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>DMT1</td>
<td>Diabetes mellitus type 1</td>
</tr>
<tr>
<td>DMT2</td>
<td>Diabetes mellitus type 2</td>
</tr>
<tr>
<td>DLCN</td>
<td>Dutch Lipid Clinic Network</td>
</tr>
<tr>
<td>E%</td>
<td>Energy percent</td>
</tr>
<tr>
<td>EAS</td>
<td>European Atherosclerosis society</td>
</tr>
<tr>
<td>FFA</td>
<td>Free fatty acids</td>
</tr>
<tr>
<td>FH</td>
<td>Familial Hypercholesterolemia</td>
</tr>
<tr>
<td>g</td>
<td>Grams</td>
</tr>
<tr>
<td>g/L</td>
<td>Gram per liter</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycosylated Hemoglobin Type A1c</td>
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<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HeFH</td>
<td>Heterozygous Familial Hypercholesterolemia</td>
</tr>
<tr>
<td>HsCRP</td>
<td>High sensitive C-reactive protein</td>
</tr>
<tr>
<td>HoFH</td>
<td>Homozygous Familial Hypercholesterolemia</td>
</tr>
<tr>
<td>IDF</td>
<td>International Diabetes Federation</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>IDL</td>
<td>Intermediate density lipoprotein</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>kg/m²</td>
<td>Kilogram per square meter</td>
</tr>
<tr>
<td>LC</td>
<td>The Lipid Clinic in Oslo</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low density lipoprotein cholesterol</td>
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LDL-R  Low density lipoprotein receptor
LDL-RAP1  Low density lipoprotein receptor adaptor protein
LLM  Lipid lowering medication
LLT  Lipid lowering treatment
LP(a)  Lipoprotein little a
LPL  Lipoprotein lipase
MetS  Metabolic syndrome
mg  Milligram
mg/L  Milligram per liter
mg/dL  Milligram per decilitre
mmHg  Millimetre of mercury
MI  Myocardial infarction
mmol/L  Millimoles per liter
n  Number of subjects
NCEP ATP III  The National Cholesterol Education Program, Adult Treatment panel III
NO  Nitrogen Oxide
OUS  Oslo Universitets Sykehus (Oslo University Hospital)
p  Point
PAR  Population attributable risk
PCI  Percutaneous coronary intervention
PCSK9  Proprotein convertase subtilisin/Kexin 9
ROS  Reactive oxygen species
SCORE  Systemic coronary risk estimation
TC  Total cholesterol
TG  Triglycerides
TIA  Transient ischaemic attack
TTT-FH  Treat-to-target Familial Hypercholesterolemia
UIO  University of Oslo
USA  United States of America
V1  The first clinical visit in the study at the Lipid Clinic
V2  The second clinical visit in the study at the Lipid Clinic
V3  The third clinical visit in the study at the Lipid Clinic
WC  Waist circumference
WHO  World’s health organization
25-75p  25th-75th percentile
%  Percent
List of tables

Table 1  The IDF and NCEP ATP III criteria’s for diagnosis of metabolic syndrome.
Table 2  Clinical characterization of the FH-population at V3
Table 3  Cardiovascular risk factors seen among the patients at V3
Table 4  Lipid lowering medication used at V3
Table 5a  Characterization of the patients without statin therapy and/or lipid lowering medications at V3
Table 5b  Blood parameters of the patients without statin therapy and/or lipid lowering medications at V3
Table 6  Blood parameters and blood pressure at V3
Table 7  Achievement of LDL-C treatment targets at V3
Table 8  Distribution of low, medium and high score for each question in the Smart Diet at V3
Table 9  Dietary supplementation used at V3
Table 10a Comparison of anthropometric data at V1 and V2
Table 10b Comparison of anthropometric data at V1 and V3
Table 11 Changes in untreated levels of TC and LDL-C to V1 and to V3
Table 12a Comparison of blood parameters and blood pressure at V1 and V2
Table 12b Comparison of blood parameters and blood pressure at V1 and V3
Table 13 Comparison of Smart Diet score at V1 and V2, and V1 and V3
Table 14 Comparison of smoking status at V1 and V2, and V1 and V3
Table 15 Comparison of age between the patients with and without CVD at V3
Table 16 Comparison of comorbidities of the patients with and without CVD at V3
Table 17 Comparison of anthropometric data of the patients with and without CVD at V3
Table 18 Comparison of blood parameters of patients with and without CVD at V3
Table 19 Comparison of lifestyle factors of the patient with and without CVD at V3
Table 20 Type and frequency of cardiovascular events before V3
List of figures

Figure 1  Flow chart with inclusion and exclusion of the participants in TTT-FH study
Figure 2  Illustration of a typical consultation in the TTT-FH study at the Lipid Clinic
Figure 3  FH diagnosis
Figure 4  Comparison of the age when starting to use lipid lowering medication for men and women
Figure 5  Adverse effects of lipid lowering medication
a) Satins b) Colesevelam
Figure 6  Reasons for not using statin therapy at V3
Figure 7  Distribution of Smart Diet categories at V3
Figure 8  Overview of the lifestyle factors at V3
a) Alcohol consumption b) Frequency of physical activity c) Intensity of physical activity d) Smoking status
Figure 9  Change in TC and LDL-C over time, from untreated to V3
Figure 10  Comparison of distribution of Smart Diet categories at V3
a) V1 and V2 b) V1 and V3
Figure 11  Smart Diet questions that changed from V1 to V2
a) Low fibre bread intake b) Meat as cold cuts c) Type of butter/margarine used on bread
Figure 12  Smart Diet questions that changed from V1 to V3
a) Vegetable intake b) Low fibre bread intake c) Fish for dinner d) Meat as cold cuts e) Type of cheese
Figure 13  Comparison of answers from the statements from V1 to V3
a) “I prefer to have as low cholesterol as possible.” b) “A healthy diet is as important as medicine.” c) “A low cholesterol is more important than not having adverse effects”
Figure 14  Development of CV events from V1 to V3
a) Number of lipid lowering medications b) Statin therapy and the use of PCSk9
Figure 15  Comparison of patients with and without CVD at V3 with regard to
a) Their age at important time stages b) TC at important time stages
Figure 16  Comparison of distribution of Smart Diet categories of patients with and without CVD at V3
Figure 17  Smart Diet questions that differentiated between those with and without CVD at V3
a) Fish used on bread b) Fish for dinner c) Type of cheese
List of appendices

Appendix 1  The Dutch Lipid Clinic Network diagnostic criteria of Familial hypercholesterolemia
Appendix 2  Study invitation with written informed consent
Appendix 3  The patient’s preference form
Appendix 5  The Clinical Report Form
Appendix 6  Approval by the Regional Committee for Medical and Health Research Ethics
1 Introduction

1.1 Cardiovascular disease
Cardiovascular disease (CVD) is the number one cause of death globally. (1) CVD is the collecting term for diseases affecting the heart and the circulatory system. Diseases of the blood vessels supplying the heart, coronary heart disease (CHD), or supplying the brain, cerebrovascular disease, are the main causes of CVD death. (2) Over 75% of CVD deaths occur in the low- and middle-income countries. (2) In Norway 8 of 10 deaths in 2012 was caused by CVD or malignant tumours. (3)

Over the last four decades, deaths caused by CVD have reduced dramatically in Norway. (4) From 1988-2012 CHD mortality decreased from 183 to 63 per 100 000 citizens, and cerebrovascular disease mortality decreased from 83 to 37 per 100 000 citizens. (3) Most of the reduction is attributed to “the cardiovascular (CV) revolution”, with better primary prevention, medications and surgical treatments. (5) Improvement in risk factors, such as cholesterol, hypertension and blood glucose, as well as in lifestyle factors, such as smoking, diet and physical activity, have also contributed to reduce the CV mortality. (4) The knowledge on the massive reduction in morbidity of CV events is insufficient, and it is difficult to say to what extent it is due to lower incidence, or lower lethality. (6)

Even with less CV mortality, the prevalence is still high. Many people experience non-lethal events, which might have a large impact on their quality of life. Therefore primary and secondary prevention of CVD disorders are a high priority in Norway, and in the rest of the world. (6) 22.september 2016, the World’s Health Organization (WHO) launched The Global Hearts Initiative that aims to reduce the global threat of CVD, including heart attacks and strokes – the world’s leading causes of death. (7)

1.2 Lipoprotein metabolism
The lipoprotein metabolism and the atherosclerosis process is complex, thus this gives just a description of the fundamental features. Triglyceride (TG) and cholesterol are two of the main lipids that circulate in the blood. They are not water-soluble so they form a complex with specialized transport mechanisms called lipoproteins, which are responsible for transporting them to cells and tissue. TG and cholesteryl esters form the core of the lipoprotein particle, and are covered by a monolayer of phospholipids, non-esterified cholesterol, and one or more
apolipoprotein (Apo), are attached to the surface of the lipoproteins, and the composition of the Apo characterizes each lipoprotein class. According to densities, determined by the relative content of lipids and proteins, lipoproteins are classified into chylomicrons (CM), very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL).

The metabolism of CM is the exogenous pathway of lipoprotein metabolism, as it distributes dietary fat from the gut to tissue and to the liver. TG and cholesteryl esters are packaged into CM, with an ApoB-48 on the surface, by the enterocytes and secreted in the circulation. In the circulation the enzyme Lipoprotein Lipase (LPL) hydrolyses TG from the CM, so fatty acids can be used for energy by the tissues. The CM are now called CM remnants and are taken up by the liver. In the liver triglyceride (TG) and cholesteryl esters are synthesised, and together with intestinally derived lipids from CM, they are packed and secreted as VLDL with an ApoB-100 on its surface. In the circulation LPL removes fatty acids from the VLDL, so it can be used in the tissue. This distribution of TG form the liver to peripheral tissue is the endogenous pathway of lipoprotein metabolism. The depleted VLDL is called IDL. IDL may be removed from the circulation by receptors on the hepatocytes, or remain in the circulation. In the circulation LPL actions shrink IDL even more, and when all the surface components except ApoB-100 is gone, IDL is converted to LDL, the predominant cholesterol-carrying particle. LDL has a long half-life in the circulation before it leaves through uptake into various tissues, particularly into the liver, through the LDL receptors (LDL-R).

HDL is formed in the circulation. HDL starts as ApoA1 molecules associated with some phospholipids, these are nascent particles called pre-β HDL. They grow by acquiring more phospholipoproteins and cholesterol from interaction with cells, or by taking the excess surface material released during the lipolysis of CM or VLDL. In contrast to LDL, will HDL remove cholesterol from the tissue and bring it to the liver for direct excretion into the bile, or to be converted to bile salts. The process is termed reverse cholesterol transport. The liver is the only organ that substantially can rid the body of cholesterol. HDL 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 these lipoproteins.

1.3 The atherosclerosis process
Atherosclerosis is a complex inflammatory process that may progress and cause CVD. It develops preferentially in vascular regions with disturbed blood flow, as they are associated
with reduced endothelial nitrogen oxide (NO) production and enhanced oxidative stress. (10) The most involved vessels are the infrarenal abdominal aorta, the coronary arteries, the popliteal arteries and the internal carotid arteries. (11) Exactly how it begins is not known.

The endothelium has direct contact to the blood flow, and is recognised to regulate several vital physiological systems. So, endothelial injury leading to dysfunction may disrupt cellular process and may be one of the first steps in the development of atherosclerosis. (12) Possible cause of damage can be shear stress, hypertension, hyperlipidaemia, toxins from cigarette smoking, hemodynamic disturbances and hypercholesterolemia. (11) Endothelial cell activation and dysfunction, will increase vascular permeability and recruit inflammatory cells, including monocytes, to the intima. Increased permeability leads to higher levels of LDL in intima. (13) LDL retention can give rise to LDL modification, including glycation, or oxidation by oxygen free radicals, generated locally by macrophages or endothelial cells. Monocytes recruited to the intima express scavenger receptors that permit uptake of modified LDL, resulting in foam cell formation, and ultimately leads to the mature lipid-laden macrophages of the plaque core. Macrophages will stimulate the release of growth factors, cytokines and chemokines, which in turn attract more monocytes and stimulate proliferation of intimal smooth muscle cells and fibroblasts. (11, 13) The subendothelial deposition of cholesterol is correlated with the level of arterial exposure to cholesterol-rich lipoproteins. (9)

A stable plaque has a densely collagenase and thickened fibrous cap with little inflammation and a small lipid core. It is unlikely to rupture, but can cause stenosis. Whereas an unstable plaque with a thin fibrous cap, large lipid core and increased inflammation is more likely to rupture and trig thrombosis leading to partial or complete vascular obstruction. (11) The process of plaque development is the same regardless of race/ethnicity or sex. The rate of development is however faster if risk factors such as hypertension, tobacco smoking, diabetes mellitus (DM) obesity, and genetic predisposition is present. (14) This is because these risk factors increase reactive oxygen species (ROS) and decrease endothelial NO production. (10)

1.4 Familial hypercholesterolemia
Familial Hypercholesterolemia (FH), first described by the Norwegian doctors Carl Müller and Francis Harbitz in the 1930s, is a common genetic cause of premature CHD. (15, 16) FH is characterized by reduced number of functional LDL-receptors. As a consequence LDL-cholesterol (LDL-C) accumulates in the circulation, which increases the risk of developing atherosclerosis. (17) The severity of atherosclerosis is proportional to the extent and duration
of elevated plasma LDL-C levels. (18) CVD due to atherosclerosis of the arterial vessel, and to thrombosis, is the foremost cause of premature mortality and of reduced disability-adjusted life years (DALYs) in Europa. It is also increasingly common in developing countries. (19)

### 1.4.1 Genetics and pathophysiology

With an autosomal co-dominant pattern of inheritance, FH will not skip a generation. A child with one heterozygote (He) parent carrying the faulty gene, have a 50% chance to inherit FH. Children with two HeFH carrier parents have a 25% chance inheriting both defect genes and therefore developing homozygous FH (HoFH). (20) The plasma levels of LDL-C in HeFH are lower, and more dependent on other genetic and environmental factors, than those with two mutated alleles, HoFH.(18) In this thesis, the use of the term FH refers to autosomal dominant HeFH unless otherwise is specified.

FH is most commonly attributed to mutations in the LDL-R gene. This gives a LDL-R with reduced function, either partial or complete, of clearing LDL-C from the circulation. Mutations in ApoB, the LDL-R binding region, or increased activity of proprotein convertase subtilisin/kexin type 9 protein (PCSK9), with subsequently increases degradation of the LDL-R, will also give hypercholesterolemia.(20-23) A loss of function PCSK9 in non-FH patients is described, and will give a higher expression of LDL-R on the cell surface and thus lower LDL-C, a protective effect on atherosclerosis. (23, 24) Autosomal recessive hypercholesterolemia, caused by mutations in LDL-R adaptor protein (LDLRAP1), is very rare. LDLRAP1 is an assumed chaperone for the LDL-R and promotes the internalization of the LDL-R/LDL-C complex into the hepatocytes. (18, 23) Over 95% of FH cases are caused by LDL-R loss-of-function mutations, ApoB mutations account for 2-5%, and gain of function mutations in PCSK9 and mutations in LDLRAP1 each account for under <1%.(23)

### 1.4.2 Prevalence

Globally an estimated prevalence of 1:500 HeFH and 1:1 000 000 HoFe is generally accepted. However recent studies have suggested that the prevalence of FH appears to be higher than commonly perceived, now up to 1:200 HeFH and 1: 300 000 HoFH. (15, 17, 25, 26) Despite the fact that FH is the most common inherited metabolic disorder, it is clearly underdiagnosed. Less than 10% are diagnosed and treated worldwide. (15) To this date, November 2017, 7690 patients have genotyped FH in Norway. This is only 30% of the assumed 25 000 people with FH. (27) 12 patients are HoFH in Norway, a prevalence of 1:440 000, which is fare closer to the newly estimate prevalence in the Netherlands, of 1:300 000, than to the globally accepted prevalence of 1:1 000 000. (26)
1.4.3 Diagnosis and clinical presentation

Too often, FH is diagnosed after the occurrence of a major CV, and not before. Yet early detection and treatment is crucial to limit premature atherosclerotic disease. In the U.S. the National Lipid Association recommends a universal screening between the ages 9 and 11 years, and no later than 20 years. A family history of hyperlipidaemia and/or premature CVD, the screening should ideally start between age 2 and 8. Several sets of criteria’s for diagnosis of FH are used, including Make Early Diagnosis to Prevent Early Death, the Simon Broome Registry and the Dutch Lipid Clinic Network (DLCN) criteria.

Based on personal and family history of premature CVD, LDL-C levels and physical examination, a numerical probability of having FH can be made. Physical signs of the disease are often specific, but not exclusive, to FH, although their absence does not rule out a diagnosis. A clinician should strongly suspect FH if the patient have: I) Tendon xanthomas, most common in Achilles tendon and finger extensor tendons, at any age. II) Arcus corneal in patients >45 years, III) tuberous xanthomas or xanthelasma in patients >20 years. The direct detection of mutations in the LDL-R, ApoB, PCSK9 and LDLRAP genes, is now also available in many countries.

If left untreated men and women with HeFH, with total cholesterol (TC) levels of 8-15 millimoles per liter (mmol/L) will typically develop CVD before age 55 and 60, respectively. HoFH with even higher TC levels, 12-30 mmol/L, typically develop CVD very early in life, and may even die before the age 20.

1.4.4 Risk factors for cardiovascular disease

FH, by itself, is a significant risk due to the lifelong exposure to high LDL-C levels. The already high risk will increase with presence of other CV risk factors, which are the same as for those without FH. A total CV risk assessment is recommended, because for most people, atherosclerotic CVD is the product of a number of risk factors. Framingham and Systemic Coronary Risk Estimation (SCORE) are two of many risk assessment systems available. Such risk estimators for the normal population will seriously underestimate the FH risk. The Montreal-FH-Score is a new score to predict CV events in FH patients.

Elevated ApoB/ApoA1 ratio, smoking, hypertension, DM, physical inactivity, low daily intake of fruit and vegetables, high alcohol consumption and psychosocial factors are nine modifiable risk factors for CVD. They account for over 90% of the population-attributed risk (PAR) for first AMI, shown in the INTERHEART study, a standardised case control...
study with close to 15,000 each of controls and cases of AMI, from 52 countries. The INTERSTROKE study, (33) also a standardised case control study, with over 10,000 cases of ischaemic stroke and over 3000 cases of intracerebral haemorrhage, and over 13,000 controls, from 32 countries. INTERSTROKE showed the same nine risk factors plus cardiac disease and depression collectively accounted for over 90% of the PAR for all stroke worldwide.

The American Heart Association has defined ideal CV health as presence of both ideal health behaviours (non-smoking, body mass<25 kilogram per square meter [kg/m²]) physical activity at goal levels, and a diet according to current guideline recommendations) and ideal health factors (TC <5.0 mmol/L, fasting blood glucose level <5.5 mmol/l and blood pressure (BP) <120 / <80 millimetres of mercury [mmHg]). (34)

The INTERHEART study inspired the Treat-To-Target Familial Hypercholesterolemia (TTT-FH) study. The TTT-FH study investigates the prevalence of modifiable CV risk factors, in a population with already increased risk of CVD due to their lifelong high lipid levels. Possessing one or more of the non-modifiable risk factors, such as high Lp(a), inflammation, aging, the male sex and family history will contribute to an increased overall risk. (35)

Elevated plasma lipids

Total Cholesterol and LDL-C
Virtually all lipid-lowering drug trials are based on TC and LDL-C, and have established that a reduction in these levels is associated with statistically and clinically significant reduction in CV morbidity and mortality. (30) A meta-analysis (36) showed that each 1.0 mmol/L reduction in LDL-C, corresponded to 10 percent (%) reduction in total and 20% in coronary mortality. Further, it also gave a 24% reduction in major CV events, including a 27% reduction in non-fatal MI, and a 25% reduction in first coronary revascularisation procedures. (36) LDL-C level <2.5 mmol/L throughout life, is associated with a low CV risk. (35)

The power of elevated LDL-C to cause CVD is most evident in the genetic forms, because even with absents of all other CV risk factors, elevated LDL-C still cause premature CVD. Thus, FH provides strong evidence for LDL being a powerful atherogenic lipoprotein. (35) Using other lipid measurements than the traditional, such as ApoB, ApoB/ApoA1-ratio and non-HDL-C, are emerging.
Elevated ApoB, ApoA and ApoB/ApoA ratio

ApoB is on the surface of all atherogenic lipoproteins, including LDL, VLDL and IDL, thus plasma level will reflect the number of cholesterol and TG-containing particles. (30, 37, 38) ApoB can be considered as an equivalent or superior to LDL-C and non-HDL. (38-40) Non-HDL, TC with HDL subtracted, is a good estimation of the total number of atherogenic particles in plasma. It may be superior to LDL-C for CV risk prediction. (37, 41) Non-HDL should not be more than 0.8mmol/L increment over the LDL-C treatment targets. (30)

ApoA1 levels are strongly correlated to HDL-C levels. (42) The Framingham study (43) showed an inverse association of HDL-C with the incidence of CHD. The reverse cholesterol transport is attributed to be the main anti-atherogenic effect of HDL, although the antioxidative, anti-inflammatory and antiapoptotic potential of HDL are also important. (38, 42) Levels less than 1 mmol/L and 1.2 mmol/L in men and women, respectively, may be regarded as a marker of increased CV risk. (30, 44) Pharmacological increasing of HDL-C, have not been successful to prove any beneficial effects on CVD. Physical activity and other lifestyle factors may be more important for increasing HDL-C levels. (44, 45)

In summary, ApoB/ApoA1 ratio reflects the balance between potentially atherogenic and anti-atherogenic lipoprotein particles, and is significantly associated with CHD death, independently of several established CV risk factors. (46, 47) The Apolipoprotein Related Mortality Risk study (AMORIS) (40), a prospective study including 175 553 middle-aged Swedish men and women, showed that ApoB/ApoA1 ratio has the largest predictive value of fatele myocardial infarction (MI) for all ages. his is consistent with the INTERHEART study, which found that the ApoB/ApoA1 ratio accounted for 42.3% of the PAR of CVD. (32) The ApoB/ApoA1 ratio should preferably be < 0.7, or even lower in FH with a high CV risk. (48)

TG

Elevated non-fasting plasma TG, a marker of elevated remnant cholesterol, is associated with increased risk of CVD and reduced HDL-C. Remnant cholesterol consists of VLDL and IDL in a fasting state, and the addition of CM in a non-fasting state. Thus TG will, in contrast to LDL-C, HDL-C and TC, increase after food intake (49-51) With TG concentrations of 2-10 mmol/L the lipoproteins are small enough to enter the arterial wall, leading to atherosclerosis. TG >10 mmol/L the risk of acute pancreatitis is greater than the risk of CVD. (52)

A doubling of non-fasting TG can give a 1.9-fold causal risk of MI. (51) A 1 mmol/L increase in remnant cholesterol is associated with a 2.8-fold causal risk for ischemic heart disease
(IHD), independent of reduced HDL. (49) This is consistent with findings in The Copenhagen City Heart Study (50) that showed a stepwise increase of non-fasting cholesterol and non-fasting TG, were similar associated with increases risk of MI and IHD. Even though TG is affected by a large number of inter-correlated variables the Prospective Cardiovascular Münster study (53) showed that TG was an independent risk factor for CHD events irrespective of serum levels of HDL-C or LDL-C. (53, 54)

$Lp(a)$

Lipoprotein a ($Lp(a)$) is a LDL-like particle with ApoB-100 linked to a Apo(a). $Lp (a)$ have enhanced atherogenic and thrombogenic properties, which increases CV risk with increased levels. (55, 56) The levels are mostly genetically determined, and the production, rather than the clearance, seems to be the major determinant of plasma levels. (55) The levels persist to be high despite intensive statins therapy. (56) Treatment with PCSK9-inhibitors, niacin or lipid apheresis, have shown to reduce $Lp(a)$ plasma levels. (57-59)

The Copenhagen City Heart Study observed a 2.6 fold increased risk for MI with $Lp(a) \geq 117$ mg/dL, when compared to <5 mg/dL. (60) With two- to three-fold elevated $Lp(a)$, observed in FH patients vs. controls, it is an independent risk factor for CVD for FH. (61, 62) The European Atherosclerosis Society (EAS) recommends a plasma level of <50 mg/dL, as an optimal level. (30) $Lp(a)$ level >30 mg/dL is consider to be a CV risk factor. (63)

Cigarette smoking

Cigarette smoking is probably the most important preventable cause of premature deaths, but it is still one of the biggest public health treats to the world. (64, 65) In year 2000, 11% of total global CV deaths were due to smoking. IHD accounted for 54% of the CV deaths attributable to smoking. (66) Even tough smoking may impact all phases of atherosclerosis the precise pathological mechanisms is not fully understood. We do know that smoking increase oxidative stress in different ways. Together with increased oxidative modification of LDL, and impairment of vasodilator function of the endothelium with reduced NO availability, increased inflammation, and lowers HDL-C. All this plays a central role in CVD. (67, 68)

Current smoking and cumulative exposure, is significant independent risk factors for CVD. (69) Odds ratio for MI was 3.0 and 2.3 for current and former smokers, respectively, compared to non-smokers in the INTERHEART study. (32) Quitting, or even reducing further smoking will be beneficial. (32, 70) Among persistent smokers, each reduction of 5 cigarettes/day, was associated with and 18% decline in mortality risk. (70)
Alcohol
Alcohol may induce both harmful and beneficial health effects, which makes it both complex and controversial. A large-scale cohort study (71), confirmed previous findings of a heterogeneous association between level of alcohol consumption and the initial presentation of CVD. A classic J shaped association for CVD and all cause mortality was seen with non-drinkers, former drinkers, and heavy drinkers whom all had increased risk compared with moderate drinkers. (71, 72) A moderate alcohol intake had a protective effect in the INTERHEART study with a PAR of 7%. (32) The assumed pathological protective mechanism for moderate alcohol consumption is the favourable changes in several CV biomarkers including significantly increased levels of HDL-C, ApoA1 and adiponectin together with significant decreased levels of fibrinogen. (73) A meta-analysis (72) concluded that an alcohol consumption of 2.5-14.9 g/day was associated with a 14-25% reduction in the risk of CVD, stroke and mortality compared to abstaining from alcohol. Higher consumption was associated with higher risks for stroke and mortality.

Abdominal obesity
An excess amount of visceral abdominal fat causes a high risk of cancer and CHD. (74) Abdominal obesity had a 28.4% PAR risk of MI in the INTERHEART study. (32) Waist-to-hip ratio had the strongest relation to risk of MI, and they are both independently related to MI. (75) Further, visceral obesity is highly correlated with insulin resistance, but measuring waist circumference (WC) will not distinguish visceral adiposity from the amount of subcutaneous abdominal fat. (30, 76) Mobilization of free fatty acids (FFA) are more rapid from visceral than from subcutaneous fat cells. (77) Increased FFA influx impairs several hepatic metabolic processes leading to hyperinsulinemia, glucose intolerance and hypertriglyceridemia. This, together with the fact that white adipose tissue secretes molecules involved in the regulation of body weight, the local inflammation generated in obesity and in vascular function, contributes to the athero-thrombotic-inflammatory abnormalities of insulin resistant. (77, 78) Obesity can however be remarkably heterogeneous, as some obese patients have normal insulin function, whereas others are sensitive or resistant to insulin. (76)

Insulin resistance is closely associated with MetS. MetS is a cluster of risk factors, including high levels of TG and blood glucose, high WC and BP, and low HDL-C, reflecting abnormalities associated with DM type 2 (DMT2), a 2-fold increased risk of CVD, CVD mortality, and stroke, and a 1.5-fold increased risk of all-cause mortality. (35, 79, 80)
Hypertension
High BP, or hypertension, is defined as a systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg. (81) Over 40% of adults over 25 years have hypertension, and under half of them are aware of it. (82) Hypertension, together with tobacco smoking and air pollution, was the leading risk factor for death and DALY lost worldwide during 2010. (83) Sustained elevation of systemic BP may impair the endothelium. Further hypertension is linked to deficient levels of NO and increased vascular production of ROS, which are key elements for the development of atherosclerosis. (84) Both Framingham and SCORE risk assessment systems includes hypertension. (30, 85) Hypertension accounted for 17.9% PAR risk of MI and 47.9% PAR of stroke in the INTRHEART and INTERSTROKE studies, respectively. (32, 33) The Systolic Blood Pressure Intervention Trial (86), concluded that intensive treatment targeting systolic BP <120 mmHg, rather than the standard <140 mmHg, reduced the risk of major CV events by 25% among patients with a high CV risk.

Consumption of fruit and vegetables
The first dietary recommendation from the Norwegian Directorate of health is: “eat a diverse diet consisting of a lot of vegetables, fruit, berries, whole grain and fish. Limit processed meat, red meat, salt and sugar.” The third is: “eat at least five portions of vegetables, fruit and berries every day”. (87) The synergic interaction and cumulative effect of this dietary pattern, which gives a high amount of essential minerals, vitamins, essential fatty acids and potential bioactive components such as antioxidants, has a beneficial effect for a good health. (88) It has an overall anti-inflammatory effect and reduced oxidative stress. (89)

A regular consumption of fruits and vegetables reduced the relative risk of MI by 30%, and lack of daily intake stood for a 13.7% PAR of MI in the INTERHEART study. (32) A meta-analysis (90) showed that CVD mortality reduced by 4% for each additional serving per day of fruit and vegetables a day combined, 5% for fruit consumption and 4% for vegetables consumption. Up to 800g/day of fruit and vegetables, especially high consumption of apples/pears, citrus fruits, green leafy vegetables/salads and cruciferous vegetables, have a risk reduction of CVD and all-cause mortality. (91)

Physical inactivity
Worldwide physical inactivity has a 6% population attributed fraction (PAF) of burden of disease due to CHD, in Norway it is 7.3%. PAF estimates the proportion of new cases that would not occur, if a particular risk factor was absent. This suggests that 7.3% of CHD could be eliminated in Norway, if all inactive people became active. (92) TPhysical activity is
therefore strongly recommended instead of a sedentary lifestyle. (88) Lack of regular daily physical activity showed a 12.2% of PAR for MI in the INTERHEART study. (32) Physical activity both prevents and helps to treat established CV risk factors, such as hypertension, insulin resistance and glucose intolerance, elevated TG concentrations, low HDL-C and obesity. (93, 94) Beneficial impact of physical activity on CVD might outweigh the negative impacts of having a body mass index (BMI) corresponding to overweight or obese, thus highlighting the risk associated with inactivity among normal weight people. (95)

**Inflammation**

Vascular inflammation occurs as a response to endothelial injury, and serum inflammation markers may predict CV risk. (96-98) The acute phase protein C-reactive protein (CRP) up-regulates adhesion molecule expression on endothelial cells and binds to ApoB-containing lipoproteins (LDL and VLDL) and is present in atherosclerotic plaque. (99) Furtermore, significant positive association between baseline common carotid artery intima media thickness and the inflammation markers CRP, fibrinogen and leucocyte count have been found. (100) The Framingham study also concluded that elevated plasma CRP could predict greater risk of ischemic stroke or trans ischaemic attack (TIA) in elderly. (98) A CRP level corresponding to low, average and high CV risk is suggested to be at levels <1milligrams per liter (mg/L), 1-3mg/L and >3mg/L, respectively. Patients with persistent unexplained marked elevation of CRP≥ 10mg/L should be examined for non-CV causes. (101).

On the other side, observations from mendelian randomizations studies indicates that a genetically raised concentrations of CRP are unrelated to the risk of CHD. (101, 102) Confounding factor, including major CV risk factors, may cause the increased CV risk seen with increased CRP, or increased CRP can be simply a marker of atherosclerosis. (102, 103) High sensitive CRP (Hs-CRP) can be used as part of a global CV risk assessment and aid in tailoring statin treatment. (101, 104) Treatment only based on Hs-CRP, is discouraged, as is the use of Hs-CRP as an alternative to major risk factors for risk assessment. (101).

**Age and sex**

The CV risk increases progressively with age, independent of sex. This is a reflection of the progressive accumulation of coronary atherosclerosis and the cumulative exposure to atherogenic risk factors. (35) However, there are important sex differences in CVD. In comparison to men, women are ten years older at their first MI, and four years older at their first stroke. (105, 106) Hypertensive disorders of pregnancy, menarche, menopause and gestational diabetes are unique risk factors for women. (107) CHD is markedly more common
in men than premenopausal woman, when traditional CV risk factors are absent. This changes in the postmenopausal state, and at that stage the CV risk is equivalent to the male sex. (107) Estrogen may have a protective role, at least in pre-menopausal women, and can explain some of the sex differences, however not all. (108) Both age and sex are crucial components of CV risk evaluation in Framingham risk score and SCORE. (30, 85)

**Diabetes mellitus**
DM is a group of diseases characterized by high fasting blood glucose and high levels of glycosylated haemoglobin type A1c (HbA1c). If the insulin production is defect, it will cause DM type 1 (DMT1). Reduced insulin utilization, or a combination of poor utilization and production, will give rise to DMT2. (109) Development of DMT2, unlike DMT1, is affected by lifestyle. DMT2 patients are typical obese and/or have abdominal obesity, which increase the flux of FFA to the liver, leading to increased insulin resistance and sensitivity. (109) A healthy lifestyle will reduce the prevalence of DMT2. (110, 111) However, the world is going in the opposite direction, and adapting a more sedentary and unhealthy lifestyle. (112)

Having DM will significantly increase the CV risk. (113) NCEP ATP III included DM as a risk factor for major coronary events equivalent to existing CHD. (35) A diabetic had a 2.37-fold higher odds ratio of MI versus a non-diabetic, and the PAR was 9.9% in the IINTERHEART study. (32) In an observational registry in the US approximately one-third of hospitalized patients with AMI had DMT2 (114) Both before and after MI, angina pectoris (AP) is more prevalent and more severe in patient with DM. (115) Some of the increased CV risk is attributed to the concurrent presence of other risk factors, such as dyslipidaemia, hypertension and obesity. Prevalence of two other CV risk factors is significant higher among adults with DM than without, regardless of CHD status. (116)

**Psychological stress**
Low socio-economic status, lack of social support, stress at work and in family life, depression, anxiety and other mental disorders contribute to the risk of developing and the worsening of the prognosis of CVD. (44, 117, 118) In the INTERHEART study psychosocial factors were integrated into a score that showed 2.4 higher odds of MI giving the PAR of MI 32.5%. (32) Mental stress has been shown to induce transient myocardial ischemia in 30-50% of patient with CAD. (119) A higher rate of CV events in the two hours following an outburst of anger was reported in a review. (120) Further, as much as every third woman and every fifth man have depression symptoms after a CV event, and depression has been positively linked to current smoking, central obesity and self-reported DM. (121) Thus, psychological
distress can influence CVD in a combination of direct and indirect methods. (122) Despite the evidence of psychological factors is associated with CHD, the underlying pathophysiological mechanisms are not fully elucidated. All the key regulatory systems including the autonomic nervous system, immune and endocrine system and components of the central nervous system may be involved, and all may impact the development of atherosclerosis. (123-125)

1.4.5 Treatment
In contrast to many genetic diseases, efficient therapy is available for FH. A combination of lipid lowering medication (LLM), and a healthy lifestyle and diet, is essential for preventing, or at least delay CV events in FH patients. (21, 22, 30, 63, 126) Ideally, the treatment should be started at age 8-10. (127) The treatment is lifelong and should be tailored to each individual, as there is individual variability in the LDL-C response to diet and LLM. (128) Four to six weeks after initiation a treatment clinical efficacy and safety should be evaluated. (15) Three months before conception, during pregnancy and lactating statin and other systemically absorbed agents are discouraged. (129)

Treatment goal
Treatment should start as soon as possible. The initial aim is a 50% reduction of untreated LDL-C levels. (22) Adult FH patients with no established CVD or DM, and who has started LLT before the age of 40, are in primary prevention with a LDL-C treatment target <2.5 mmol/L. An even lower treatment target, <1.8 mmol/L, are for those in secondary prevention with established CVD, DM or who were untreated before the age of forty. (19, 30, 126, 130) LDL-C should be less than 3.5 mmol/L, in children and youth under 18 years old. (130)

Lipid lowering medicine

Statin
Statin is the first choice of pharmacological treatment to reduce LDL-C. (15) Statin inhibits hydroxymethylglutaryl-coenzyme A in the liver, reducing the synthesis of cholesterol and thereby up-regulates LDLR on the hepatocyte surface. This will increase uptake of LDL-C from the blood and decrease plasma LDL-C, together with other Apo-containing lipoproteins in the plasma. (22, 30) Statins have an anti-inflammatory effects mediated by inhibition of macrophages, in addition to lowering lipids. (131) The most potent statin is Rosuvastatin, followed by Atorvastatin, Simvastatin, Lovastatin, Pravastatin and Fluvastatin. (30).

In a meta-analysis (132) of 174 000 participants, statins reduced the risk of CV events by 21% for every 1.0 mmol/L decrease in LDL. Reduction in CV mortality is also reported. (133-135) Further health benefits found is a 30-50% reduction of TG, 5-10% increase in HDL-C, and a
reduction in BP. (30, 136) However, adverse effects from statin are reported, and are dose-dependent and vary among statins. An international survey (137), estimated that 6% of patient with hypercholesterolemia would have symptoms associated with statin therapy. Of them 72% were reported to present with muscle-related symptoms.

Low potency statins are generally inadequate in FH patients and maximum potent statin should be started at first consultation because very few reach their LDL-C target. (15) Optimal starting age is debated. It is suggested a consideration at age 8-10 years and should ideally start before 18 year of age.(22, 129) On the other hand, a follow-up study showed that carotid inter media thickness will increase 0.003mm in FH patient for each year that statin therapy is postponed, indicating that an earlier initiation of screening and treatment will give a greater benefit, and perhaps also a better compliance in the future. (138)

**Ezetimibe**
Ezetimibe targets Niemann-Pick C1-like protein 1, thereby inhibits intestinal absorption of dietary and biliary cholesterol, without affecting the absorption of fat-soluble nutrients. The liver up-regulates LDLR on the hepatocytes, and this leads to increased LDL-C uptake from the blood and subsequently a decreased plasma concentration. (30) Used in monotherapy LDL-C reductions of 15-22% in hypercholesterolemic patients are observed. (30) Clinical studies supports Ezetimibe to be used as second –line therapy combined with statins when therapeutic goals is not achieved as the maximal tolerated statin dose. (129) A simple doubling of statin dose can give a 6% decrease in LDL-C, but an addition of Ezetimibe will however give a 15-20% reduction in LDL-C. (139) The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (140), showed that the Ezetimibe added to statin therapy after an acute cardiac stroke reduced LDL-C, 1.4 mmol/L versus 1.8 mmol/L in the simvastatin- monotherapy, and improved CV outcome. Furthermore ischaemic stroke was reduced by 21%. In Europe and the United States of America (USA), Ezetimibe is approved from 10 years of age, and is very well tolerated with minimal side-effects. (127)

**Bile acid sequestrants**
Resin is a bile acid sequestrant, which binds to bile salts preventing the enterohepatic reuptake of bile. The liver is forced to use intracellular cholesterol to make more bile acid. This induce increased LDLR on the hepatocyte, and subsequently the plasma LDL-C is reduced. (22) It is the only documented safe LLM during breastfeeding and pregnancy. (35, 141) In maximum doses it can reduce LDL-C up to 25%, but it is often associated with some
gastrointestinal problems. (30) It is recommended to use after introduction of statin and Ezetimibe treatment as a third LLM for those who need further LDL-C reduction. (30, 142)

**PCSK9 inhibitor**

PCSK9 degrades LDLR protein, and thereby inhibiting PCSK9 has been shown to be an effective strategy to reduce LDL-C. Up to 40-60% reduction have been shown. (143) It is an established option for use in mono-therapy for those with statin intolerance, or as an addition to traditional LLM. In the general population PCSK 9-inhibitors, in the addition to statin treatment, will substantially decrease LDL-C further and reduce the risk of CV death and MI. (144) FH patients, with even higher baseline levels, will most likely draw even more benefits of PCSK9-inhibitors. The cost effect has impact on the restricted rules of reimbursement of this medicine. (145) Currently there are a lot of on-going studies on PCSK9-inhibitors effect on CV events and mortality, and the future will tell the significance of this new era medicine.

**Diet and lifestyle recommendations**

Diet is the first-line therapy and the mainstay of treatment for dyslipidaemia in all ages, and especially in childhood. (127) It may influence atherogenesis directly, or through traditional CV risk factors, including hypertension, blood lipids, abdominal obesity and glucose levels. (19) This makes diet a crucial component for health promotion. (126)

**Chose unsaturated fat, rather than saturated fat**

Saturated fat is the dietary factor with the strongest impact on LDL-C levels. (146) The daily saturated fat intake should be less than seven percent of the total daily energy requirement (E%), for a maximum LDL-C lowering effect of the diet. (35) The most beneficial for reducing CV risk is not just decreasing the amount of saturated fat, but replacing it with polyunsaturated fat. (146, 147) If 1 E% from saturated fat is replaced by monounsaturated fatty acids, LDL-C decreases by 4.1%, and a 5.1% reduction is seen if replaced by polyunsaturated fatty acids instead. (146) EAS conclude that CVD reduces 2-3% with every reduction in saturated fat that is substituted with polyunsaturated fat. (148, 149) A low fat diet whit mainly unsaturated fat can be achieved by eating low fat dairy products, lean and fatty fish two to three times a week, nuts, choosing vegetable oils in cooking, with the exception of palm- and coconut oils, use avocados, olives, mayonnaise or oil spreads and dressing, and limit the intake of fatty and processed meat. (148, 150, 151)

These dietary choices are consistent with a Mediterranean dietary pattern, which has a strong protective association against CHD and MI, compared to the harmful factors found in trans fatty acids and foods with a high glycaemic index or load, and a western dietary pattern. (152)
Similarly, the strong evidence of causation with a Mediterranean dietary pattern is compatible with findings in both the Lyon Heart Study (153), conducted in France in the late 1980s, and the Prevention with Mediterranean Diet study (89), conducted in Spain from 2003-2009.

**Chose food rich in fibre**
Dietary fibres, found in high amounts in legumes, fruits, vegetables and whole grain cereal, are all part of a Mediterranean dietary pattern, and have a direct hypocholesterolaemic effect. Water-soluble fibres can reduce TC and LDL-C by 5-10%. (30, 154) Further, dietary fibres have cardio-protective benefits such as lowering BP, improve blood glucose control, weight loss, improve immune function and reduce inflammation. (154) In a pooled analysed cohort (155), every 10g/d increment of dietary fibre was associated with a 14% risk reduction in all coronary events, and a 27% decrease in coronary death. A intake of 25-40g per day, including high amount of soluble fibre, is recommended. (30, 88) Furthermore an intake of functional food added plant sterols/stanols, such as the Vita hjertego ‘proactive margarine, may have beneficial effects and should be considered as 2 g/d of plant sterols/stanols can reduce LDL-C by 8-10%. (35, 148, 150)

**Limit intake of sugar, salt and food naturally high in cholesterol**
The intake of certain foods should be limited. Sugary containing beverages, sweets, candy, ice cream and other foods rich in sugar, contain a high amount of sugar and calories. Sugar should not exceed 10% of total energy intake. (149, 150) An intake above this level may contribute to excess energy intake and subsequently development of obesity, if not matched with a high physical activity level. Obesity and especially visceral fat is linked to increase risk of MetS and developing of DMT2. (77, 112) Further, salt should be limited to <5g/day. This implies to reduce food seasoning, but also processed foods high in salt content. This should be most stringent for people with hypertension. (30, 150) Also food with naturally high cholesterol, such as shrimps, egg yolk and non-filter coffee, may raise cholesterol values. Even if the magnitude of the increase may vary between individuals, a moderate intake is recommended. (150)

**Be physical active, do not smoke or drink excess amount of alcohol**
The Nordic Nutrition recommendations are a 150 minutes of moderate intensity physical activity throughout the week, or at least 75 minutes of vigorous-intensity physical activity throughout the week, or engage in an equivalent combination of moderate- and vigorous-intensity activity. (88) Further, smoking should be discouraged with immediate effect. If not successful at first attempt, the physician should continue to advocate for stopping, or at least reducing the number of cigarettes smoked a day, and the exposure to second hand smoking.
(28) With regard to alcohol, the recommended level is less than 10-20g a day, or 1-2 units a day. The energy contribution from alcohol should not exceed 5 (E%) intake for adults. (88) Advice about alcohol intake should be individualized with religion, culture, environment and personal beliefs in mind, as regularly moderate alcohol consumption might evolve to heavy drinking. (32)

1.5 Gaps in the knowledge of FH
Early detection and treatment is recognized to play a crucial role for the treatment of FH, and would delay the onset of premature CVD. Effectiveness of LLM and a healthy lifestyle on CV risk are confirmed in non-FH patients, and to some degree also in FH patients. The recommendations for FH patients are therefore to start an intensive treatment as early as possible, the same with developing healthy dietary and lifestyle habits. The treatment should never stop. The treatment targets and recommendations are all updated on regular basis, as there are coming new studies on benefits of early detection and intensive treatment.

However, what is scarcely described in the literature is how much of these recommendations are actually followed and achieved by the FH patients. How many do actually get an early diagnosis, and what is the mean age for diagnosis and starting with LLM? Are there any differences between the sexes, or for those who have already established CVD? Furthermore, do the FH patients eat healthy and are they physical active enough? Are we able to document improvements in the patients with regard to lipid values, health, diet and lifestyle, after years of consultations with physicians and clinical nutritionists at a specialized Lipid Clinic?

This thesis will try to answer some of these questions, and will describe the FH population with regard to what they have achieved after an intensive treatment over many years. This is very important because, in order to sharpen the treatment for FH and to withstand future CVD, it is important to know what have been archived and where the potentials for improvements are, and what might still be the main driving forces of accelerated CVD.
2 Aim of the study

2.1 Thesis rationale
The TTT-FH study is a prospective study, of the treatment of FH patients given at the Lipid Clinic (LC), Rikshospitalet, Oslo University Hospital (OUS). This thesis, the third in this study, aims to increase the number of participants and continue the observation of what is achieved after an intensive LLT given at the LC, with a special focus of the prospective period of eight to ten years, started by Marlene Thorvall in 2014 and followed by Irene Mork in 2016. (156, 157) This thesis will further include the age aspect of this FH population with regard time of diagnosis and the time they started using LLM.

The thesis starts with a description of the current state at visit 3 (V3) with regard to lipid values and other blood parameters, achievements of treatment targets, the use of medication, adverse effects of medication, patients off statin therapy, and the dietary and lifestyle factors. In addition the age when they were aware of their FH diagnosed, and when they started using LLM is calculated. The focus in the second part is to describe if there have been any changes during the study, and the last part is dedicated to compare those with and without CVD at V3, especially focusing on the time aspect of awareness of FH, LLM start, MetS, diet and lifestyle factors.

2.2 Thesis objectives
1. Describe the FH-population at V3 regarding:
   a. Age at FH-diagnosis and the age they started to use LLM.
   b. Type and intensity of the LLM, use of antihypertensive and glucose lowering medication.
   c. Type and prevalence of adverse effects related to LLM.
   d. Patients off statin therapy regarding sex, length of time without statins, 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 MetS.
   h. Diet, physical activity level, smoking status and alcohol consumption.
2. Study if treatment at the LC, with special focus on the study period, resulted in changes regarding:
   a. Lipid values, fasting glucose and HbA1c.
   b. Weight and WC.
c. Diet, physical activity level, smoking status and alcohol consumption.

d. The patients preferences towards:
   i. A healthy lifestyle relative to medical treatment.
   ii. Having as low cholesterol as possible.
   iii. A low cholesterol level relative to accepting having adverse effects.

3. Study if there are any differences between the patients with and without CVD at V3, concerning:
   a. Age at awareness of FH-diagnosis and when they started to use LLM.
   b. Type and intensity of LLM, use of antihypertensive and glucose lowering medication.
   c. Untreated cholesterol levels, and cholesterol levels and levels of fasting glucose and HbA1c.
   d. Weight and WC.
   e. Occurrence of abdominal obesity and MetS.
   f. Diet, physical activity level, smoking status and alcohol consumption.

2.3 Hypothesis
An intensive LLT over eight to ten years is hypothesized to results in a further reduction in cholesterol levels, favourable trends concerning diet, lifestyle, body weight, WC and glycaemic control. Furthermore, patients with CVD at V3 are hypothesized to have a higher burden of CV risk factors than patients not having any CVD at V3.
3 Subjects and methods

3.1 Recruitment of participants

3.1.1 Enrolment and the first visit
In 2006, from the 9th of January until 9th of July, adult patients were continuously invited to participate in the TTT-FH study during their routine consultations at the LC.

Inclusion criteria’s were:

i. Patient at the LC with a FH diagnosis verified by a genetic test or the DLCN criteria’s (appendix 1). (15, 158, 159)

ii. Between 18 and 75 years old.

Exclusion criteria’s were:

i. Participants in other on-going project with unknown medication or intervention.

ii. Unable to follow the consultations scheduled.

iii. Pregnant or lactating.

iv. Did not take LLM due to hypersensitive or experienced serious adverse effects. (Note, this was not an exclusion criteria at V3, only at enrolment.)

The consultation they were invited, served as their first visit (V1) in the study. The study was at start considered to be a quality study, and therefore needed no approval form the Regional Ethical Committee. Figure 1 shows a summarized version of the implementation of the participants in the TTT-FH study, with the flow of inclusion and exclusion of the participants. During the study period the patients were scheduled for their regular consultations at the LC independent of the projects. The frequency of consultations was determined by the different doctors, and varied from each year to every third year.

3.1.2 The second visit
All the participants from V1 were invited to a second clinical visit (V2) at the LC by telephone or letter. V2 was conducted during 2007 as a follow-up median one year after V1.

3.1.3 The third visit

Visit three part I
100 patients were invited by mail to V3 part I in the fall of 2014. Of them 20 patients were no longer on the LC waiting lists. They were telephoned and invited to participate in the study by mail. 64 patients were included in the analysis, and the results presented in the published 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”, published in May 2015. (157)
Visit three part II
The patients who did not attended V3 part I, and the 25 patients excluded after V1, formed the basis of V3 part II. The patients who came to their routine consultation at the LC after V3 part I where continuously invited to V3 part II. The rest of the patients were sent invitations to participate based on the waiting list of the LC, in the spring 2016. The 156 patients who had finished V3, either part I or part II, were included and analysed in the published master thesis by Irene Mork - “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 patient with Familial Hypercholesterolemia”, in November 2016. (156)

Visit three part III
The patients who had not attended V3 part I or II, or where excluded from the other Master theses analyses, formed the basis for V3 part III. The patients who came to their routine consultation at the LC after V3 part II, where continuously invited to V3 part III. The rest of the patients still attending the LC were sent invitations according to the waiting list of the LC. The invitation (Appendix 2) consisted of an ordinary consultation summon, information about the study, implications of the study, and a written consent they had to sign to participate. 12 patients were on the waiting list for late in 2017-2019. Due to capacity and to the respect of the waiting list system at the LC these were not invited to V3.

10 of the participants were overlooked, and not invited when they met to routine consultations during 2016. To lessen the burden for them, by having to come for a new consultation and take new blood samples, an invitation for a telephone interview together by mail. The written consent was signed and sent back if the wanted to participate. The master student, Karoline Randsborg, called them one week after the invitations were sent. The telephone interview, conducted by the master student, was completed by eight of the patients. The patient’s medical record from the last consultation was used, and the telephone interview was used to get supplementary information, answering the patient’s preference schema (appendix 3) and going through the Smart Diet questionnaire (appendix 4). The last two patients were not reached after three calls on three different days. A message was left after each call asking to call back if they wanted to participate to, but they did not.

Furthermore, nine of the participants were already in another on-going project at the LC. The study was open with a known medication and dose so they were all, except two, contacted by telephone and asked if they wanted to continue their participating in the TTT-FH. All of the seven contacted were included. Of the two not contacted, one was very sick and the other did
not show up for the follow-up consultation on the other study and was not reached afterwards. Of the 62 patients who completed V3 part III one did not attend V2, and to others patients were excluded from the analyses. One was treated with LDL-apheresis and one was lactating.

Figure 1. Flow chart with inclusion and exclusion of the participants in the TTT-FH study. V1 was conducted in 2006, V2 in 2007 and V3 over three periods in 2014, 2016 and 2017. n indicates number of subjects. TTT-FH Treat To Target Familial Hypercholesterolemia, V1 visit 1, V2 visit 2, V3 visit 3, LC the lipid clinic.
3.2 Materials

3.2.1 Collection of data
The methods used for data collection was the same for all the visits during the TTT-FH study. At V1 and V2, all the doctors at the LC participated in the data collection and followed the same protocol. For all parts of V3 one doctor (dr Kjell Erik Arnesen), held the majority of the consultations together with a master student in clinical nutrition that differed for each part. The three master students had good contact and coordinated themselves to ensure that the data collection occurred in the same way for each part. **Figure 2** illustrates a typical consultation in the TTT-FH study, with the exception of the consultation with the master student, which only took place at V3. 38 patients at V3 part II and 14 patients at V3 part III did not receive a separate consultation with a master student because they were invited to V3 when they came for their routine consultation and at that time the Master students had not started their thesis.

**Figure 2** Illustration of a typical consultation in the TTT-FH study at the Lipid Clinic.

* The Patient’s preference form was not included at V2
b A master student was not present at V1 or V2

TTT-FH Treat to Target Familial Hypercholesterolemia, BP blood pressure

Any missing information in the forms was collected from the patient’s medical record to the furthest extent. Some of the information in the patient’s medical record was not sufficiently according to dates or values, therefore a set of plotting rules was used. Winter was plotted as 15th of January, spring as 15th of May, summer as 15th of July and fall as 15th of October, for the given year. If just a year was stated, 30th of June was plotted. If a month was stated the 15th of that month was plotted. If an interval of several years or months was stated the 30th of the median month and/or year was plotted. If a decade was stated the 30th of June of the fifth
year of that decade was plotted. Puberty was set as age 13 for men and 12 for women. If a value was indicated as an interval, the mean value was plotted.

**Blood parameters**

Most patients used a prefilled laboratory requisition and took blood samples two weeks prior to the consultation, or soon after. Fasting blood samples were drawn and centrifuged within two hours of admission. The majority of the blood samples were analysed at the Department of Medical Biochemistry, Rikshospitalet, OUS, the rest were analysed at local laboratories.

The following assay methods apply to the blood analysed at the Department of Medical Biochemistry. All levels were measured in plasma, TC and TG was measured with an enzymatic colorimetric assay, while LDL-C and HDL-C was measured with a homogenous enzymatic calorimetric assay. CRP was measured by particle reinforced immunoturbidimetric assay and serum-glucose was measured enzymatic with hexokinase. All analyses were carried out on Cobes 8000, c/02. ApoA1 and ApoB were measured by turbidometry on Cobas c501. The instruments, reagents and calibrator were delivered from Roche Diagnostics (Mannheim, Germany). All analyses, except LDL-C, were accredited after International and European standard NS-EN ISO 15189.

The laboratory results for TC, LDL-C, HDL-C, TG, CRP, ApoB, ApoA1, fasting glucose and HbA1c, at each visit were obtained from the patient’s medical records. At V3 part III the master student went through all the medical records and obtained the highest Lp(a) value ever measured from the patients medical record. The majority of the patients had not analysed their Lp(a) regularly, some only once or a few times in their life. The master student calculated ApoB/ApoA1 ratio and non-HDL-C. Untreated TC and LDL-C was collected from their medical record. The master student at V3 part III went through all the patient’s medical records to double check all first known untreated TC and LDL-C levels. In this thesis only untreated TC and LDL-C from the same blood sample were registered. In those cases were only TC, HDL-C and TG were analysed, and were TG was <4.5 mmol, Friedwalds formula was used to calculate LDL-C. The date when the first known untreated levels were taken was also registered at V3 part III and used to calculate the age at first measured TC. (160)

Concerning CRP, some laboratories measured regular CRP, and others Hs-CRP. Regular CRP is adequate for monitoring severe inflammatory conditions, but do not have the sensitivity to measure levels accurately within the range needed for cardiac risk detection like Hs-CRP assay. (161)The collected data had therefor a huge gap in sensitivity. Some laboratories
reported that CRP was under a certain level (<5, <1 or <0.6), others reported 0 as a value, where’s others again reported Hs-CRP with exact levels as low as 0.20 mg/L. Therefore, CRP levels are presented as stratified levels according to what the statement, from Centre’s for Disease Control and Prevention and The American Heart Association, defined as low, average and high CV risk, which corresponds to levels of CRP at <1mg/L, 1-3 mg/L and >3mg/L respectively. (101)

A digital BP device of the brand Welch Allyn® Vital Signs Monitor 300 series (Welch Allyn, USA) was used for BP measurements of the patients at V3. At V1 and V2 BP was measured with other, but calibrated digital BP devices. The patient rested three minutes before BP was measured three times with three minutes intervals. The last measurement was reported.

**Anthropometric data**
Either the doctor or the master student measured the anthropometric data with the same equipment for the majority of the patients at V3. At V1 and V2 other calibrated weights and equipment from the LC was used, but some of the patients self reported the weight. The weight was measured by an electronic body weight, Soehnle® 7720 SR 202763 (Soehnle, Germany). The patients were weighted without shoes, belts, heavy jewellery, phones and with light clothing. Height was measured by a stadiometer, Seca® 222 (Seca, United Kingdom). The patients stood straight against the wall and with heels touching the wall. BMI was calculated dividing weight in kilogram (kg) by height in squared meters. WC was measured with a non-stretchable tape over the unclothed abdomen midway from the lower rib margin to the anterior superior iliac crest, while the patient was standing and breathing calmly.

**Medication, adverse effects and potential endpoints**
The Clinical report form (appendix 5) 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. During the consultation the doctor filled out most of the form, but some information was obtained from the patient’s medical records. The form consists of five pages.

The first part describes type, intensity and duration of medications, including pharmacological treatment of hypertension, DM and other non-LLM. At V3 part III the master student went through all the medical records to make a timeline for continued medication. The start date of the LLM, including statin, Ezetimibe, resin, high dose omega-3, niaspan, hypocol and PCSK9-inhibitors, which were continued until V3 were collected. Changes in dose, or strength in the same LLM category was not taken to consideration. A break for over 6 months
was regarded as discontinuation, this included pregnancy and lactation if LLM were not used. The age when single, double, triple and quadruple LLM started was calculated by subtracting the patient birthday from the starting date of the LLM. Furthermore, the length of LLM used prior to pregnancy for women, and the length of the discontinued period due to conceiving-pregnancy and lactation, were calculated.

Further, possible adverse effects from each LLM used at V3 were described. The doctor decided, based on patient history and the dialog with the patient at V3, what kind of adverse effect the patient described and most likely which medication that caused it.

An adverse effect was classified as:
- **Definitive**: if it disappeared with discontinuation of the medication, and reoccurred with initiation of the same medication. Retesting was often done several times over the years, resulting in a definite impression of both the patient and the doctor of an adverse effect.
- **Probable**: Somewhat less certainty than definitive.
- **Possible**: If there was uncertainty about the relation of the adverse effect to the LLLM.

The adverse effects were categorized based on which organ system they affected.
1. **Gastrointestinal**: Flatulence, diarrhoea, constipation and stomach pains.
2. **Muscle**: muscle pain, muscle stiffness and asthenia.
3. **Neurological**: headache, wilt and numbness.
4. **Psychological**: Anxiety, nervousness and depression.
5. **Sexual problems**: impotence.
6. **General /other**: Malaise, dyssomnia.

The second page describes interruptions of LLM and registration date at the LC. The third page describes adverse event after last visit. Page four was partly complementary to the Smart Diet, with assessment of social status and lifestyle. The fifth, and last page, addressed CV endpoints, such as AMI, death, coronary revascularization procedures like coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), documented AP, hospitalization with primary diagnosis of congestive heart failure, cerebrovascular events, first diagnosis of peripheral vascular disease, hospitalized due to peripheral vascular disease, or other non-CHD vascular events. 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 peacemaker.
Diagnosis of metabolic syndrome

The definitions from the International Diabetes Federation (IDF) and the NCEP ATP III were both used to diagnose MetS. (35, 80) The criteria’s are summarized in table 1.

Table 1. The IDF and NCEP ATP III criteria’s for diagnosis of MetS.

<table>
<thead>
<tr>
<th>Diagnosis of MetS</th>
<th>IDF</th>
<th>NCEP ATP III</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC + any two criteria’s</td>
<td>WC &gt; 94 cm for men, &gt; 80 cm for women</td>
<td>WC ≥ 102 cm for men, ≥ 88 cm for women</td>
</tr>
<tr>
<td>TG ≥ 1.7 mmol/L</td>
<td>≥ 1.7 mmol/L</td>
<td>≥ 1.7 mmol/L</td>
</tr>
<tr>
<td>HDL &lt; 1.0 mmol/L for men, &lt; 1.3 mmol/L for women</td>
<td>&lt; 1.0 mmol/L for men, &lt; 1.3 mmol/L for women</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose ≥ 5.6 mmol/L or treatment for DM</td>
<td>≥ 5.6 mmol/L or treatment for DM</td>
<td></td>
</tr>
<tr>
<td>Blood pressure ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or Antihypertensive treatment</td>
<td>≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or Antihypertensive treatment</td>
<td></td>
</tr>
</tbody>
</table>

IDF International Diabetes Federation, ATP The National Cholesterol Education Program, Adult Treatment panel III, MetS metabolic syndrome, WC waist circumference, cm centimeters, TG triglyceride, mmol/L millimoles per liter, HDL high density lipoprotein, DM diabetes mellitus, mmHg millimeters of mercury.

Diet and lifestyle

Dietary and lifestyle data were collected with the Smart Diet. It is a questionnaire developed by the LC, aiming to evaluate how cardio protective the diet is. The LC has used it since 2004 in daily consultations, both at new and follow-up consultations. It is self-instructive, easy to use and takes about ten minutes to complete. It is validated for all ages. (162, 163) The first part evaluates the cardio protective potential of the diet. Based on total score, the patient is categorized as either having “healthy dietary habits”, “potential for improvements on some areas” or “potential for improvements in several areas”. Part two addresses lifestyle factors including smoking status, alcohol consumption and physical activity. These are non-scoring questions, which are open for subjective assessments.

Smart Diet versions

Due to an improved availability to different foods, and the continuous development of new products, the Smart diet has been revised two times, in 2007 and 2009, since the first version in 2003. A third revision is in progress. For comparison reasons the 2003 version was used at all visits. However due to sampling errors 18 patients did not answer the Smart Diet, and 102 had a newer version of Smart Diet at V2. At V3 15 did not have the 2009 version, and one did not answer a Smart Diet questionnaire at all.

The Smart Diet version 2003

All the Smart Diet questions, for all the patients at all the visits in the TTT-FH study, were recounted and categorized at V3 part III by the master student. The intention was to look closer at all the individual question in the Smart Diet, and to see what specific dietary choices
that changed during the study, and what separated those with and without CVD. The analyses of V3 part I and II in the two former Master theses had collected the questions into subgroups of dairy, meat, fish, fruit and vegetables. They did not look at the questions that included cereals, and food or beverages with a high content of sugar.

The Smart Diet version 2003 has 15 questions concerning choice of food, with three alternatives giving 1-3p. The questions are both qualitative and quantitative. The questions about milk, sour cream, cheese, fat used on bread/crisps, fat used in cooking and meat as cold cuts or for dinner, are scored according to fat content. The other questions, about low fibre bread, fish used on bread and as dinner, mayonnaise, fruit, juice and berries, vegetables, sweet bread spreads and soft drinks and chocolate/cake/biscuits, are scored according to frequency. The total score gives an impression of the overall diet. The higher the score, the more cardio protective the diet is. The individual questions pinpoints where the improvements should be done. Maximum score is 45p. \( \leq 29p \) is low and defined as “potential for improvements on several areas”, 30-37p is medium, and defined as having “potential for improvements on some areas” and \( \geq 38p \) is high and indicates “healthy dietary habits”.

**Smart Diet and sampling error**

The patient filled out the Smart Diet in the waiting room prior to the consultation. The answers were used as a template for a discussion with the doctor, or the dietary counselling with a clinical dietician at V1 and V2. At V3, the master student evaluated the Smart Diet and discussed the answers with the patients, and corrected if there were any misunderstandings. 52 patients did not see a master student at V3, so their Smart Diet was not discussed further.

If a patient had ticked off for more than one alternative for the same question, the patient was given a mean score for the given question. The patient’s total score was used to categorize them into the Smart Diet categories high, medium and low. It was also used to calculate the mean total score for all the patients, used in comparison of the Smart Diet at each visits and when comparing the patients with and without CVD.

Further analyses of each question of the Smart Diet were done. The distribution of 1p, 2p and 3p for the same question was compared for the different visits, and between the patients with and without CVD at V3. For these analyses the patient had to score 1p, 2p or 3p, and not be in-between two scores. The patients, who had ticked off twice, in 1p and 3p scores, were scored 2p at that question. Those who had ticked off twice at the same question, and where
the difference was one point, was counted into two groups. Those who had ticked off for 1p and 2p were one group, and those who ticked off for 2p and 3p, were another group. Half of the patients in each group were given the lowest score, and the other half the highest score at the given question. So, as one group the total score remained the same at that question. If the group contained an uneven number of patients, one more patient was given the lowest score, so the total score as a group for that question was half a point less than true registered score.

In the case of missing answers, total score was not calculated. However, data may still be available regarding the Smart Diet categories, if the missing value did not affect the final category. If a patient had already filled out a 2009-version, this was used as a template to fill out the 2003-version together with the master student. In the telephone interviews at V3 part III, the master student used the 2003-version of Smart Diet and filled out the answered during the interview of the patient.

**Lifestyle factors**
Smoking was categorized as yes or no, and number of cigarettes smoked daily “five or less”, “six to ten”, “eleven or more” or “party smoker”, if they smoked, at all visits. Smoking status prior to study enrolment was also gathered from their medical records. Alcohol consumption was assessed, and categorized into “never” or how many units of alcohol consumed per week; “less than one”, “one to seven”, “eight or more”. One unit was defined as 125mL wine, 330 mL beer or four cL of spirits. Physical activity was categorized based on number of sessions’ á 30 minutes, or more, a week with exercise; “never”, “less than one”, “once to twice” or “three or more”, and the intensity; “high”, “moderate” or “combination of high and moderate”. Endurance training and high intensity resistance training was classified as high intensity, while resistance training and brisk walking was classified as moderate intensity. Use of dietary supplements was classified into “non”, “cod-liver oil”, “omega-3 capsules”; “multivitamins” and “other “.

**Patients preference form**
The patient’s preference form (Appendix 3) is a non-validated questionnaire developed by the LC, in 2006, especially for this study. It addresses to which extent the patients are satisfied with the treatment and follow-up offered by the LC, furthermore their attitude towards different statements regarding living with FH. In this master thesis the questions regarding diet, medications and adverse effects are in focus. The first statement is “I think that lifestyle improvements are equally important as the use of LLM”. The second statement is if the patient wishes “his or hers cholesterol level to be as low as possible”, and the third statements
is 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 in the TTT-FH study was voluntary, and a participant could at any time, without stating a reason, withdraw from the study. At each visit the patients read and signed a written informed consent (Appendix 2) 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 LC, where only employees have access. All the data presented here in this master thesis, previous master thesis and presentations on the TTT-FH study, are anonymous and cannot be traced back to the one specific patient. The Regional Ethical Committee for Medical Research have given approval for this master thesis (Appendix 6).

3.2.2 Statistical methods

All statistical analysis was carried out by IBM SPSS version 24.0.0.0 (SPSS Inc, Chicago). The variables were continuously double-checked during the plotting process, to control for errors. In addition, extreme values were double-checked, and descriptive analysis was run to check random variables. Missing data was handled by giving it a blank cell in SPSS.

Descriptive analysis was preformed at V3, and analytic analysis of the three visits. Continues variables were checked for normal distribution by inspection of histograms, normal Q-Q plot and detrended Q-Q-plots. If the continuous variables were normal distributed, the mean (95% confidence interval [95% CI]) was presented. If the continuous variable were skewed, median (25th-75th percentiles [25-75 p] was presented, or the minimum and maximum value. Categorical variables were presented as number of cases and percentages (%). In the analytic analysis, normal distributed continuous variables measured at the different visits were analysed by a paired t-test to detect differences. If the distribution were skewed the non-parametric Wilcoxon Signed Rank test were used. V1 was tested against V2 and V3 separately. For categorical variables, cross tabulation and frequency analysis was carried out. For detecting differences between two, three or more ordinal variables measured at the different visits, Wilcoxon Signed Rank test was used. For detecting differences between two, three or more nominal variables measured for the same patients at different visits, McNemers test or McNemar-Bowker test of symmetry was used, respectively. In the cases with small sampling sizes Fischer’s exact test was used. The analytic results are presented in tables, were
number of measured individuals differs for each variable due to different number of missing data at each variable at the three visits.

Analytic comparison of patients with and without CVD at V3 was also performed. Normal distribution of continues variables were analysed by an independent t-test for detecting differences, while skewed distributed of continuous variables were analysed with the non-parametric 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, or the sampling number was small, Fisher’s exact two-tail probability test was used. Missing values were handled by pairwise exclusion. Conducting Bonferroni adjustments for multiple testing on this master thesis was not used, since this master thesis is 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 characterization of the 216 patients who fulfilled the TTT-FH study is summarized in table 2 and 3, and figure 3. Mean (95% CI) age was 52.4 years (50.7, 54.0) and 53.7% were male. First known measured high TC was at mean (95% CI) age 26.8 years (25.0, 28.5), and the first visit to the LC at a mean (95% CI) age of 33.3 years (31.3, 35.3). (Data not shown). Mean BMI for men and women were 27.4 kg/m² and 26.8 kg/m², respectively. 69 patients were diagnosed with MetS, either based on the NCEP ATP III or the IDF criteria. (Data not shown). 63 patients had experienced one or more CV event. 9.8% used glucose lowering medication and 28.2% used antihypertensive medication. 92% of the patient had a genetically verified FH diagnosis.

Table 2. Clinical characterization of the FH-population at V3.

<table>
<thead>
<tr>
<th>Number of attending subjects at V3, n=216</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(^{a})</td>
</tr>
<tr>
<td>Male</td>
<td>116</td>
</tr>
<tr>
<td>Female</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>n(^{a})</td>
</tr>
<tr>
<td>Age at V3, years</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>116</td>
</tr>
<tr>
<td>Women</td>
<td>100</td>
</tr>
<tr>
<td>Age at first visit to LC, years</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>116</td>
</tr>
<tr>
<td>Women</td>
<td>100</td>
</tr>
<tr>
<td>Age at first measured high TC, years</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>111</td>
</tr>
<tr>
<td>Women</td>
<td>100</td>
</tr>
<tr>
<td>Height, cm</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>116</td>
</tr>
<tr>
<td>Women</td>
<td>100</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>116</td>
</tr>
<tr>
<td>Women</td>
<td>100</td>
</tr>
<tr>
<td>BMI, kg/m(^{2})</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>116</td>
</tr>
<tr>
<td>Women</td>
<td>100</td>
</tr>
<tr>
<td>Waist, cm</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>106</td>
</tr>
<tr>
<td>Women</td>
<td>81</td>
</tr>
</tbody>
</table>

Data are given as mean (95% CI).

\(^{a}\)Indicates total number of analysed subjects.

FH Familial Hypercholesterolemia, CI Confidence interval V3 Visit 3, LC the Lipid Clinic in Oslo, TC total cholesterol, cm centimetres, kg kilograms, BMI body mass index, kg/m\(^{2}\) kilograms per square meter.
Figure 3. FH diagnosis

Data are shown as % and n indicates number of analysed subjects.

FH diagnosis
- Genetical verified
- Clinical definite
- Clinical probably
- Clinical possible

Table 3. Cardiovascular risk factors seen among the patients at V3.

<table>
<thead>
<tr>
<th>Cardiovascular risk factors</th>
<th>n²</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>104</td>
<td>37 (35.6)</td>
</tr>
<tr>
<td>Women</td>
<td>81</td>
<td>49 (60.5)</td>
</tr>
<tr>
<td>Metabolic syndrome defined by the NCP ATP III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>114</td>
<td>25 (21.9)</td>
</tr>
<tr>
<td>Women</td>
<td>96</td>
<td>32 (33.3)</td>
</tr>
<tr>
<td>Metabolic syndrome defined by the IDF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>103</td>
<td>30 (29.1)</td>
</tr>
<tr>
<td>Women</td>
<td>79</td>
<td>29 (36.7)</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>116</td>
<td>40 (34.5)</td>
</tr>
<tr>
<td>Women</td>
<td>100</td>
<td>23 (23.0)</td>
</tr>
<tr>
<td>Glucose lowering medication</td>
<td>216</td>
<td>21 (9.7)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>216</td>
<td>61 (28.2)</td>
</tr>
</tbody>
</table>

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

n² indicates total number of analysed subjects.

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

NCP ATP III criteria’s for diagnosis of MetS. (35)

IDF criteria’s for diagnosis of MetS. (80)

CV cardiovascular; V3 Visit 3, NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III, IDF International Diabetes Federation.

4.1.2 Lipid lowering medication

Type and number of LLM

Table 4 shows the LLM used at V3. 16 patients were without statin therapy, and 11 patients completely out of LLM. 17 patients used PCSK9-inhibitors. The vast majority used high intensity statin treatment either as single medication, or as part of a double, triple or quadruple medication. Over half of the patients used a double LLM and the statin-Ezetimibe combination was used of almost all. One out of four used triple LLM, of which four out of five used the statin- Ezetimibe -colesevelam combination.
Table 4. Lipid lowering medication used at V3.

<table>
<thead>
<tr>
<th>Number of attending subjects at V3, n=216</th>
<th>n</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statin therapy</td>
<td>216</td>
<td>16 (7.4)</td>
</tr>
<tr>
<td>High intensity statin therapy(^b)</td>
<td>216</td>
<td>168 (77.8)</td>
</tr>
<tr>
<td>Moderate intensity statin therapy(^c)</td>
<td>216</td>
<td>32 (14.8)</td>
</tr>
<tr>
<td>Ezetimibe(^d)</td>
<td>216</td>
<td>175 (81.0)</td>
</tr>
<tr>
<td>Colesevelam(^e)</td>
<td>216</td>
<td>55 (25.5)</td>
</tr>
<tr>
<td>PCSK9-inhibitor(^f)</td>
<td>216</td>
<td>17 (7.9)</td>
</tr>
<tr>
<td>High dose omega-3(^g)</td>
<td>216</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Niaspan</td>
<td>216</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Hypocol(^b)</td>
<td>216</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>No LLM</td>
<td>216</td>
<td>11 (5.1)</td>
</tr>
<tr>
<td>Single LLM</td>
<td>216</td>
<td>29 (13.4)</td>
</tr>
<tr>
<td>Statin</td>
<td>29</td>
<td>26 (92.9)</td>
</tr>
<tr>
<td>Ezetrol</td>
<td>29</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Hypocol</td>
<td>29</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Double LLM</td>
<td>216</td>
<td>111 (51.4)</td>
</tr>
<tr>
<td>Statin and Ezetimibe</td>
<td>112</td>
<td>108 (96.4)</td>
</tr>
<tr>
<td>Statin and colesevelam</td>
<td>112</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Statin and high dose omega-3(^g)</td>
<td>112</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Ezetimibe and PCSK9-inhibitor</td>
<td>112</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Triple lipid LLM</td>
<td>216</td>
<td>57 (26.4)</td>
</tr>
<tr>
<td>Statin, Ezetimibe and colesevelam</td>
<td>57</td>
<td>46 (80.7)</td>
</tr>
<tr>
<td>Statin, Ezetimibe and PCSK9-inhibitor</td>
<td>57</td>
<td>7 (12.3)</td>
</tr>
<tr>
<td>Statin, Ezetimibe and high dose omega-3(^g)</td>
<td>57</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td>Statin, colesevelam and PCSK9-inhibitor</td>
<td>57</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Quadruple LLM</td>
<td>216</td>
<td>8 (3.7)</td>
</tr>
<tr>
<td>Statin, Ezetimibe, colesevelam and PCSK9-inhibitor</td>
<td>8</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Statin, Ezetimibe, colesevelam and niaspan</td>
<td>8</td>
<td>1 (12.5)</td>
</tr>
</tbody>
</table>

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

\(^a\)Indicates total number of measured subjects.
\(^b\)High statin therapy is defined as: atorvastatin 40-80mg or rosuvastatin 20-40mg
\(^c\)Moderat statin therapy is defined as: atorvastatin 10-20mg, rosuvastatin 5-10mg, pravastatin 40-80mg, simvastatin 20-40mg, lovastatin 40mg, fluvastatin 40mg, pitvastatin 2-4mg.
\(^d\)Ezetimibe dose was 10mg.
\(^e\)Colesevelam dose 370mg n=2, 375mg n=1, 1250mg n=3, 1875mg n=6, 2188mg n=1, 2500mg n=5, 3125mg n=2, 3750mg n=24, 4375mg n=11.
\(^f\)Repatha 140mg n=6, Praluent 75mg n=7, Praluent 150mg n=4.
\(^g\)Defined as >1000mg. 1000mg n=1, 2000mg n=2, 3000mg n=1.
\(^h\)Hypocol is a red yeast rice, a nature preparation classified as a medical drug due to the small content of naturally occurring monakoliner.(164)

**Age and sex differences at LLM start**

Figure 5 shows the timeline for continued medication divided by sex. 97.4% of the men and 92.0% of the women reported to use LLM. Among those 90.3% of the men and 80.4% of the women had two types of medication. Among those with double medication 48.0% of the men and 21.6% of the women increased to triple medication later on. Only 16.8% of the men increased to quadruple medication. (Data not shown) Mean (95% CI) age of starting
medication was 34.7 years (32.8, 35.9). The men were 31.9 years (32.8, 34.0), and the women were 37.8 years (35.6, 39.9 95).

22 of the women discontinued their on-going LLM due to pregnancy, but started again thereafter. Average length of LLM used before the child period was 7.9 years (5.8, 10.0 95% CI) and time off LLM was 4.2 years (3.2, 5.3 95% CI). The rest of the women were either not on LLM due to other reasons than pregnancy or lactation (n=4), did not have children (n=14), did not know their cholesterol before after forty years of age (n=16) or started LLM after childbirth (n=44). (Data not shown).

No significant sex differences were seen in the age of starting double or triple medication, but the men started at an earlier age in both situations. Mean (95% CI) 43.7 years (41.4, 46.0) vs 46.5 years (44.1, 48.9) for double medication and 49.5 (46.7, 52.4) vs 54.5 (48.9, 60.0) for triple medication. Only men used quadruple medication and the mean age for starting with was 53.4 (43.8, 62.9).

4.1.3 Adverse effects

Adverse effects form statin therapy and colesevelam therapy are shown in figure 6. 33.5% of the statin users reported adverse effects, mainly muscular pains. In colesevelam users 27.3% reported adverse effects, and mainly gastrointestinal problems. Of the other LLM only one patient had probable gastrointestinal adverse effects of Ezetimibe, and one patient had definite
adverse effects of PCSK9-inhibitor. Of the five patients who used high dose omega-3, the one person who used nicotinic acid and the one who used Hypocol there were no one who reported adverse effects.

Figure 6. Adverse effects of lipid lowering medication
a) Statin therapy  b) Colesevelam therapy at V3.
* Classified as definite, probable or possible in a pre-specified form filled in by a physician
Definite: The adverse effect disappeared with the discontinuation of the medication and reoccurred with initiation of the same 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.
© Statin therapy definite n=13, probable n=26 and possible n=14, Colesevelam therapy possible n=1
© For statin definite n=1, probable n=5 and possible n=2, for colesevelam definite n=4, probable n=8 and possible n=2
© Definite n=1, probable n=5
© Probable n=1
© Possible n=1

4.1.4 Patients without statin therapy and/or lipid lowering medication
16 patients, twelve women and four men, did not use statin at V3, mainly due to adverse events of previous treatment regime (figure 7). Three of the sixteen patients had not yet restarted statin therapy after pregnancy and lactation. With the exception of these three women, table 5a shows the characterization of the 13 patients without statin treatment, and table 5b their blood values at V3. 8 of these 13 patients did not use any LLM at all at V3. The median time since last statin treatment was 4.0 years, the shortest time was one month, and the longest was 16 years. Time without LLM was at median time 1.5 years. Three of patients had experienced a CV event. Of these three, two used antihypertensive medication and one had MetS. Of those who had not experienced CVD, one used antihypertensive medication and two had MetS. Two patients used the combination of Ezetimibe and PCSK9-inhibitor. Two patients used Ezetimibe, as a single medication, and another patient used Hypocol, as a single medication. Seven of the patients, five whom did not use any LLM, were ready to restart a new regime of statin treatment at V3.
Figure 7. Reasons for not using statin therapy at V3.
Data are given as number. n indicates number of analysed subjects.

Table 5a. Clinical characterization of the patients without statin therapy and/or LLM at V3.

<table>
<thead>
<tr>
<th>Without statin therapy</th>
<th>Without any LLM</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(^{a})</td>
<td>n (%)</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>Genetically verified FH diagnosis</td>
<td>13</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>13</td>
</tr>
<tr>
<td>Hypertension treatment</td>
<td>13</td>
</tr>
<tr>
<td>Metabolic syndrome(^{b})</td>
<td>13</td>
</tr>
<tr>
<td>LLM</td>
<td></td>
</tr>
<tr>
<td>Non</td>
<td>13</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>13</td>
</tr>
<tr>
<td>PCSK9-inhibitor</td>
<td>13</td>
</tr>
<tr>
<td>Hypocol</td>
<td>13</td>
</tr>
<tr>
<td>Restarted statin at V3</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 5b. Age and blood parameters of the patients without statin and/or LLM at V3.

<table>
<thead>
<tr>
<th>Without statin therapy</th>
<th>Without any LLM</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(^{a})</td>
<td>Median (min, max)</td>
</tr>
<tr>
<td>Age, year</td>
<td>13</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>12</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>12</td>
</tr>
<tr>
<td>ApoB, mmol/L</td>
<td>12</td>
</tr>
<tr>
<td>ApoA1, mmol/L</td>
<td>12</td>
</tr>
<tr>
<td>Ratio ApoB/ApoA1</td>
<td>12</td>
</tr>
<tr>
<td>Lp(a), mg/L</td>
<td>12</td>
</tr>
<tr>
<td>Time off treatment(^{c}), year</td>
<td>13</td>
</tr>
<tr>
<td>Time on statin, year</td>
<td>13</td>
</tr>
</tbody>
</table>

Data are given as number (%) and median (min, max).

\(^{a}\) Indicates total number of measured subjects.

\(^{b}\) Diagnosed based on the IDF and/or NCEP ATP III criteria’s.

\(^{c}\) Time since last statin treatment for all 13 patients, then time since last LLM ended for those 8 patients without LLM.

LLM lipid-lowering medication, V3 Visit 3, PCSK9-inhibitor proprotein subtilisin/kexin type 9-inhibitor, TC total cholesterol, mmol/L millimoles per liter, LDL-C low-density lipoprotein cholesterol, ApoB apolipoprotein B, g/L grams per liter, ApoA1 apolipoprotein A1, Lp(a) lipoprotein little a, mg/L milligrams per liter. NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III, IDF International Diabetes Federation.

4.1.5 Blood parameters
Blood lipids and BP at V3 are shown in table 6. The median Lp (a) level was 295.5mg/L with a 25-75p from 122.5 to 783.3 mg/L, lowest at 8 mg/L and highest at 5500 mg/L. (Data not shown). Regarding CRP 66.0% had <1mg/L, 18.0% had 1-3 mg/L and 16.0% measured >3 mg/L, where 8.3% of them were over 10 mg/L. (Data not shown).
Table 6. Blood parameters and blood pressure at V3.

<table>
<thead>
<tr>
<th>Number of attending subjects at V3, n=216</th>
<th>nᵃ</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mmol/L</td>
<td>216</td>
<td>5.0 (4.8, 5.2)</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>216</td>
<td>3.0 (2.9, 3.2)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>216</td>
<td>1.4 (1.4, 1.5)</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>215</td>
<td>1.1 (1.1, 1.2)</td>
</tr>
<tr>
<td>ApoA1, g/L</td>
<td>205</td>
<td>1.5 (1.5, 1.6)</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>207</td>
<td>1.1 (1.0, 1.1)</td>
</tr>
<tr>
<td>Ratio ApoB/ApoA1</td>
<td>205</td>
<td>0.7 (0.7, 0.8)</td>
</tr>
<tr>
<td>Non-HDL-C, mmol/L</td>
<td>216</td>
<td>3.6 (3.4, 3.8)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>204</td>
<td>5.6 (5.3, 5.8)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>184</td>
<td>5.7 (5.6, 5.8)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>199</td>
<td>128.1 (126.5, 129.8)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>199</td>
<td>77.2 (76.0, 78.4)</td>
</tr>
</tbody>
</table>

Data are given as mean (95%CI) or median (min, max).  
ᵃIndicates total number of measured subjects.  
V3 visit 3, CI confidence interval, TC total cholesterol, mmol/L millimoles per liter LDL-C low-density lipid cholesterol, HDL-C high density cholesterol, TG triglycerides, ApoA1 apolipoprotein A1, g/L gram per liter, ApoB apolipoproteinB, , HbA1c glycosylated Hemoglobin type A1c, BP blood pressure, mmHg millimetre of mercury.

4.1.6 Achievement of LDL-C treatment goal

Table 7 shows achievement of different LDL-C treatment targets, and the last part of the table those close to achieving the targets are included.

Table 7. Achievement of LDL-C treatment targets at V3.

<table>
<thead>
<tr>
<th>Number of attending subjects in V3, n=216</th>
<th>nᵇ</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50% reduction in LDL-C from untreated values</td>
<td>89</td>
<td>68 (76.4)</td>
</tr>
<tr>
<td>Total &lt;2.5 mmol/L in LDL-C</td>
<td>216</td>
<td>78 (35.9)</td>
</tr>
<tr>
<td>Total reached LDL-C treatment goalᵇ</td>
<td>216</td>
<td>45 (20.1)</td>
</tr>
<tr>
<td>Primary prevention, LDL-C &lt;2.5 mmol/Lᶜ</td>
<td>122</td>
<td>37 (30.3)</td>
</tr>
<tr>
<td>Secondary prevention, LDL-C &lt;1.8 mmol/Lᵈ</td>
<td>94</td>
<td>8 (8.5)</td>
</tr>
<tr>
<td>Without PCSK9-inhibitor</td>
<td>8</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>With statin therapyᶜ</td>
<td>200</td>
<td>45 (22.5)</td>
</tr>
<tr>
<td>Achieves, or close to achieving LDL-C treatment goalᵇ</td>
<td>216</td>
<td>84 (38.9)</td>
</tr>
<tr>
<td>Primary prevention, LDL-C &lt;2.5 mmol/Lᶜ</td>
<td>122</td>
<td>60 (49.2)</td>
</tr>
<tr>
<td>Secondary prevention, LDL-C &lt;1.8 mmol/Lᵈ</td>
<td>94</td>
<td>24 (25.5)</td>
</tr>
<tr>
<td>Without PCSK9-inhibitor</td>
<td>24</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>With statin therapyᶜ</td>
<td>200</td>
<td>84 (42.0)</td>
</tr>
</tbody>
</table>

Data are given as number (%).  
bIndicates number of patients the target applies to.  
bTargets are according to the guidelines from the European Atherosclerosis Society. (30)  
cApplies to patients without CVD, DM or diagnosed later than 40 years of age.  
dApplies to patients with CVD, DM or diagnosed later than 40 years of age.  
e15% increased LDL-C above treatment goal from the guidelines from the European Atherosclerosis Society.  
fEither used as a single medication or in combination with other LLMs  
V3 visit 3, LDL-C low-density lipid cholesterol, mmol/L millimoles per liter, PCSK9-inhibitor proprotein subtilisin/kexin type 9-inhibitor, CVD cardiovascular disease, DM diabetes mellitus. LLM lipid lowering medication.
4.1.7 Dietary and lifestyle factors

Dietary factors
Average Smart Diet score was 36.2 points (35.7, 36.7% 95CI), of a maximum 45p (data not shown). The distribution of a low, medium and high score, which corresponds to 1p, 2p and 3p, respectively, to each questions are summarized in table 8. The majority scored in the middle Smart Diet category. Two out of five were in the highest category (figure 8). Dietary suppletions used at V3 are summarized in table 9.

Table 8. Distribution of low, medium and high score for the Smart Diet questions at V3.

<table>
<thead>
<tr>
<th>Food group</th>
<th>n(^a)</th>
<th>Low (1p) n (%)</th>
<th>Medium (2p) n (%)</th>
<th>High (3p) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk(^b)</td>
<td>213</td>
<td>2 (0.9)</td>
<td>121 (56.8)</td>
<td>90 (42.3)</td>
</tr>
<tr>
<td>Sour cream(^b)</td>
<td>213</td>
<td>5 (2.3)</td>
<td>66 (31.0)</td>
<td>142 (66.7)</td>
</tr>
<tr>
<td>Cheese(^b)</td>
<td>210</td>
<td>72 (34.3)</td>
<td>78 (37.1)</td>
<td>60 (28.6)</td>
</tr>
<tr>
<td>Butter/margarine on bread(^b)</td>
<td>211</td>
<td>14 (6.6)</td>
<td>19 (9.0)</td>
<td>178 (84.4)</td>
</tr>
<tr>
<td>Fat in cooking(^b)</td>
<td>212</td>
<td>7 (3.2)</td>
<td>26 (12.0)</td>
<td>179 (82.5)</td>
</tr>
<tr>
<td>Mayonnaise products(^c)</td>
<td>212</td>
<td>122 (57.5)</td>
<td>14 (6.6)</td>
<td>76 (35.8)</td>
</tr>
<tr>
<td>Low fibre bread(^ad)</td>
<td>212</td>
<td>21 (9.9)</td>
<td>-</td>
<td>191 (90.1)</td>
</tr>
<tr>
<td>Meat as cold cuts(^b)</td>
<td>211</td>
<td>7 (3.2)</td>
<td>21 (10.0)</td>
<td>183 (86.7)</td>
</tr>
<tr>
<td>Meat for dinner(^b)</td>
<td>212</td>
<td>2 (0.9)</td>
<td>42 (19.8)</td>
<td>168 (79.2)</td>
</tr>
<tr>
<td>Fish on bread/ crisps(^c)</td>
<td>211</td>
<td>69 (32.7)</td>
<td>84 (39.8)</td>
<td>58 (27.5)</td>
</tr>
<tr>
<td>Fish for dinner(^c)</td>
<td>211</td>
<td>46 (21.2)</td>
<td>98 (45.2)</td>
<td>67 (30.9)</td>
</tr>
<tr>
<td>Vegetables(^c)</td>
<td>196</td>
<td>58 (29.6)</td>
<td>93 (47.5)</td>
<td>45 (23.0)</td>
</tr>
<tr>
<td>Fruit/berries/juice(^c)</td>
<td>196</td>
<td>67 (34.2)</td>
<td>80 (40.8)</td>
<td>49 (25.0)</td>
</tr>
<tr>
<td>Sweet spread and sweet drinks(^c)</td>
<td>207</td>
<td>4 (1.9)</td>
<td>11 (5.3)</td>
<td>192 (92.8)</td>
</tr>
<tr>
<td>Candy, chocolates, biscuits, ice cream etc.(^c)</td>
<td>207</td>
<td>12 (5.8)</td>
<td>88 (42.5)</td>
<td>107 (51.7)</td>
</tr>
</tbody>
</table>

Data are given as number and percentage n (%).
\(^a\)Indicates total number of measure subjects
\(^b\)Questions based on saturate fat content.
\(^c\)Questions based on frequency.
\(^d\)There were only possible to score one or three points.
V3 visit 3, p points.

Figure 8. Distribution of Smart Diet categories at V3.
Data are given as %.
\(^a\)A Smart Diet score ≥ 38 p, ≥ 31 p or ≥ 36 p in the 2003-, 2007- or 2009- version of Smart Diet respectively.
\(^b\)A Smart Diet score 30-37 p, p, 25-30 p or 28-36 p in the 2003-, 2007- or 2009- version of Smart Diet respectively.
\(^c\)A Smart Diet score ≤ 29 p, ≤ 24 p or ≤ 27 p in the 2003-, 2007- or 2009- version of Smart Diet respectively.
Table 9. Dietary supplements at used V3.

<table>
<thead>
<tr>
<th>Attending subjects at V3 n=216</th>
<th>n a</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non</td>
<td>204</td>
<td>129 (63.2)</td>
</tr>
<tr>
<td>Cod-liver oil</td>
<td>204</td>
<td>52 (25.5)</td>
</tr>
<tr>
<td>ω-3 capsules</td>
<td>204</td>
<td>61 (29.9)</td>
</tr>
<tr>
<td>Multivitamin</td>
<td>204</td>
<td>28 (13.7)</td>
</tr>
<tr>
<td>Other</td>
<td>204</td>
<td>34 (16.7)</td>
</tr>
</tbody>
</table>

Data are given as number (%).

*a* Indicates total number of measured people.

*b* Calculated only based on the subjects who filled out the 2003-version of Smart Diet.

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

### Lifestyle factors

**Figure 9** shows the current smoking status, alcohol consumption and physical activity level at V3. 14.2% were smokers at V3, with a median smoking time of 34.5 years, with the shortest period of 7.0 years and the longest for 53.0 years. Close to half of the non-smokers had been smokers before, and they had a median smoking time of 14.0 years, the shortest was around one year and the longest up to 46 years. Half of the patients reported an alcohol consumption of 1-7 units a week, and 13% did not drink alcohol. Half of the patient reported a physical activity level ≥ 3 times a week. One out of five reported zero or less than one session a week. Most of the physical activity level was reported to be of moderate intensity.

**Figure 9. Overview of lifestyle factors at V3**

a) Alcohol consumption  
b) Frequency of physical activity  
c) Intensity of physical activity  
d) Smoking status

Data are given as % and n indicates number of analysed subjects

*a* Given as units. One unit is defined as 125 ml wine, 330 ml beer or 4 cl. spirits.

*b* Given as number of session, where one session was >30 minutes.

*c* High intensity is equal to endurance training, a moderate intensity activity is equal to brisk walking and resistance training, a mixed intensity is a mixture of endurance training and resistance training.

*d* 85 patients (46.7%) of the non-smokers at V3 had been smokers earlier in life with a median smoking time in years (min, max): 14 (1, 46).

*e* Median smoking time, year (min, max): 34.5 (7, 53).
4.2 Changes in cardiovascular risk factors

4.2.1 Anthropometric data
Both men and women increased their weight and WC significantly (p<0.05) during the study (table 10).

<table>
<thead>
<tr>
<th>Attending subjects</th>
<th>V1</th>
<th>V2</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>89</td>
<td>86.7</td>
<td>86.7 (83.7, 89.7)</td>
<td>88.3 (85.1, 91.5)</td>
</tr>
<tr>
<td>Women</td>
<td>79</td>
<td>72.7</td>
<td>72.7 (69.3, 76.1)</td>
<td>74.3 (70.8, 77.8)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>89</td>
<td>26.4</td>
<td>26.4 (25.6, 27.3)</td>
<td>26.9 (26.1, 27.8)</td>
</tr>
<tr>
<td>Women</td>
<td>79</td>
<td>25.2</td>
<td>25.2 (24.0, 26.4)</td>
<td>25.8 (24.7, 26.9)</td>
</tr>
<tr>
<td>Waist, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>21</td>
<td>97.4</td>
<td>97.4 (93.5, 101.3)</td>
<td>99.3 (95.1, 103.6)</td>
</tr>
<tr>
<td>Women</td>
<td>24</td>
<td>89.7</td>
<td>89.7 (84.9, 94.6)</td>
<td>92.5 (87.4, 97.6)</td>
</tr>
</tbody>
</table>

Table 10b. Comparison of anthropometric data at V1 and V3

<table>
<thead>
<tr>
<th>Attending subjects</th>
<th>V1</th>
<th>V3</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>98</td>
<td>86.2</td>
<td>86.2 (83.4, 88.9)</td>
<td>90.0 (86.7, 93.2)</td>
</tr>
<tr>
<td>Women</td>
<td>89</td>
<td>72.2</td>
<td>72.2 (69.1, 75.3)</td>
<td>75.4 (72.0, 78.8)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>98</td>
<td>26.7</td>
<td>26.7 (25.8, 27.5)</td>
<td>27.8 (26.9, 28.8)</td>
</tr>
<tr>
<td>Women</td>
<td>89</td>
<td>25.5</td>
<td>25.5 (24.5, 26.6)</td>
<td>26.7 (25.6, 27.8)</td>
</tr>
<tr>
<td>Waist, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>30</td>
<td>96.8</td>
<td>96.8 (92.7, 101.0)</td>
<td>101.8 (95.5, 108.1)</td>
</tr>
<tr>
<td>Women</td>
<td>23</td>
<td>89.4</td>
<td>89.4 (84.4, 94.4)</td>
<td>95.2 (90.7, 99.8)</td>
</tr>
</tbody>
</table>

Data are given as mean (95% CI).

For calculation of p-value, paired t-test was used. *Significant change at p<0.05
V1 visit 1, V2 visit 2 kg kilograms, kg/m² kilograms per square meter, cm centimetres, V3 visit 3

4.2.2 Blood parameters
The remarkable decrease from untreated blood values of TC and LDL-C, to blood values at V3 are illustrated in figure 10 as a timeline, and shown in table 11. In average a 50.0% reduction from untreated values was seen at V3. The other blood values for V1 to V3 are summarized in table 12. TG, ApoA1, ApoB, blood glucose and HbA1c all increased significantly (p<0.05) from V1 to V3. The other blood values were quit stable during the study.
Figure 10. Change in TC and LDL-C over time, from untreated to V3.

Data are given as mean with 95% CI as error bars and n indicates number of analysed subjects

<table>
<thead>
<tr>
<th>Attending subjects</th>
<th>n = 216, missing values TC n = 6 and LDL-C n = 127</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attending subjects</td>
<td>n = 216, missing values TC n = 5 and LDL-C n = 21</td>
</tr>
<tr>
<td>Attending subjects</td>
<td>n = 216, missing values TC n = 1 and LDL-C n = 1</td>
</tr>
<tr>
<td>Attending subjects</td>
<td>n = 206, missing values TC n = 1 and LDL-C n = 2</td>
</tr>
<tr>
<td>Attending subjects</td>
<td>n = 216, no missing values.</td>
</tr>
</tbody>
</table>

mmol/L millimoles per liter, TC total cholesterol, LDL-C low density lipoprotein, LC the lipid clinic in Oslo, Norway, V1 visit 1, V2 visit 2, V3 visit 3.

Table 11. Changes in untreated levels of TC and LDL-C to V1 and to V3.

<table>
<thead>
<tr>
<th>Attending subjects</th>
<th>n</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>% Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mmol/L</td>
<td>210</td>
<td>10.0 (9.7, 10.3)</td>
<td>5.6 (5.4, 5.8)</td>
<td>43.6%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>89</td>
<td>7.6 (7.1, 8.1)</td>
<td>3.9 (3.6, 4.2)</td>
<td>48.0%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>211</td>
<td>10.0 (9.7, 10.3)</td>
<td>5.0 (4.8, 5.2)</td>
<td>50.0%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>89</td>
<td>7.6 (7.1, 8.1)</td>
<td>3.2 (2.9, 3.5)</td>
<td>57.9%</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

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

*Indicates total number of measure subjects.

V1 Visit 1, V3 visit 3, CI Confidence interval, TC Total cholesterol, mmol/L millimoles per liter, LDL-C Low-density lipoprotein cholesterol.

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

*Significant change at p<0.05

Table 12a. Comparison of blood parameters and blood pressure at V1 and V2.

<table>
<thead>
<tr>
<th>Attending subjects</th>
<th>V1</th>
<th>V2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>216</td>
<td>206</td>
<td></td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>204</td>
<td>4.3 (4.0, 4.5)</td>
<td>3.8 (3.7, 4.0)</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>204</td>
<td>5.6 (5.4, 5.9)</td>
<td>5.2 (5.0, 5.3)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>204</td>
<td>0.1 (-0.1, 0.1)</td>
<td>0.0 (0.0, 0.0)</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>200</td>
<td>1.0 (0.9, 1.1)</td>
<td>1.0 (0.9, 1.1)</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>193</td>
<td>1.2 (1.0, 1.1)</td>
<td>1.0 (0.9, 1.0)</td>
</tr>
<tr>
<td>ApoA1, g/L</td>
<td>196</td>
<td>1.4 (1.4, 1.4)</td>
<td>1.4 (1.4, 1.4)</td>
</tr>
<tr>
<td>Ratio ApoB/ApoA1</td>
<td>193</td>
<td>0.8 (0.7, 0.8)</td>
<td>0.7 (0.7, 0.8)</td>
</tr>
<tr>
<td>Non-HDL, mmol/L</td>
<td>204</td>
<td>5.1 (5.0, 5.2)</td>
<td>5.2 (5.1, 5.4)</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>182</td>
<td>5.4 (5.4, 5.5)</td>
<td>5.5 (5.4, 5.6)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>156</td>
<td>128.8 (126.2, 131.5)</td>
<td>127.1 (125.0, 129.3)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>143</td>
<td>78.3 (76.4, 80.2)</td>
<td>77.8 (76.2, 79.3)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>143</td>
<td>78.3 (76.4, 80.2)</td>
<td>77.8 (76.2, 79.3)</td>
</tr>
</tbody>
</table>

The table continues on the next page.
Table 12b. Comparison of blood parameters and blood pressure at V1 and V3.

<table>
<thead>
<tr>
<th>Attending subjects</th>
<th>V1</th>
<th>V3</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n*</td>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>215</td>
<td>5.6 (5.4, 5.8)</td>
<td>5.0 (4.8, 5.2)</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>215</td>
<td>3.9 (3.7, 4.1)</td>
<td>3.0 (2.9, 3.2)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>215</td>
<td>1.4 (1.3, 1.5)</td>
<td>1.4 (1.4, 1.5)</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>212</td>
<td>1.0 (0.9, 1.0)</td>
<td>1.2 (1.1, 1.2)</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>198</td>
<td>1.0 (1.0, 1.1)</td>
<td>1.1 (1.0, 1.1)</td>
</tr>
<tr>
<td>ApoA1, g/L</td>
<td>199</td>
<td>1.4 (1.3, 1.4)</td>
<td>1.5 (1.5, 1.6)</td>
</tr>
<tr>
<td>Ratio ApoB/ApoA1</td>
<td>198</td>
<td>0.8 (0.7, 0.8)</td>
<td>0.7 (0.7, 0.8)</td>
</tr>
<tr>
<td>Non-HDL, mmol/L</td>
<td>215</td>
<td>4.2 (4.0, 4.4)</td>
<td>3.6 (3.4, 3.8)</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>191</td>
<td>5.1 (5.0, 5.2)</td>
<td>5.6 (5.4, 5.8)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>162</td>
<td>5.4 (5.3, 5.5)</td>
<td>5.7 (5.6, 5.8)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>154</td>
<td>128.4 (125.9, 130.9)</td>
<td>128.9 (127.0, 130.9)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>153</td>
<td>78.0 (76.2, 79.7)</td>
<td>77.1 (75.7, 78.6)</td>
</tr>
</tbody>
</table>

Data are given as mean (95% CI) for all variables
*Indicates total number of measured subjects.

BP blood pressure V1 Visit 1, V2 Visit 2, V3 Visit 3, CI Confidence interval, TC Total cholesterol, mmol/L millimoles per liter, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, TG triglycerides, ApoA1 apolipoprotein A1, g/L grams/liter, ApoB apolipoprotein B, HbA1c Glycosylated Hemoglobin Type A1c, mmHg millimetres of mercury

P-value was calculated with paired sample t-test. *Significant change at p<0.005.

4.2.3 Dietary and lifestyle factors

Dietary factors

Comparison of Smart Diet score and distribution of Smart Diet categories from all the visits are shown in table 13 and figure 11, respectively. With the exception of ω-3 capsules, which reduced by 30% from V1 to V3, there were no other significant (p<0.005) changes in dietary supplementation consumption. (Data not shown) The single Smart Diet questions that significantly (p<0.005) changed from V1 to V2, and V1 to V3 are shown in figure 12 and figure 13, respectively. No other significant (p<0.005) changes were seen in the Smart Diet questions (data not shown).

Table 13 Comparison of Smart Diet score between V1 and V2, and V1 and V3.

<table>
<thead>
<tr>
<th>n*</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V1</td>
<td>V2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smart Diet score(^b), (p)</td>
<td>66</td>
<td>35.5 (34.5, 35.6)</td>
<td>36.4 (35.6, 37.2)</td>
<td>0.9 (0.6, 1.8)</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>V3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smart Diet score(^b), (p)</td>
<td>166</td>
<td>35.3 (34.7, 35.9)</td>
<td>36.1 (35.5, 36.6)</td>
<td>0.8 (0.2, 1.3)</td>
</tr>
</tbody>
</table>

Data are given as mean (95% CI) or number (%).
*Indicates number of measured subjects.
\(^b\)Only Smart Diet version 2003 was used, maximum score was 45p.
\(^p\)For calculation of p-value paired t-test was used. *Significant change at p<0.05
V1 Visit 1, V2 Visit 2, V3 visit 3, Smart Diet Smart Diet, CI Confidence interval.
Figure 11: Comparison of distribution of Smart Diet categories at a) V1 and V2 b) V1 and V3. Data are given as %. n indicates number of measured subjects. P-value was calculated with McNemar Bowker test. *Significant difference at p-value <0.05.

Figure 12: Smart Diet questions that changed from V1 to V2. a) Low fibre bread intake b) Meat as cold cuts c) Type of butter/margarine used on bread. Data was collected from the Smart Diet questionnaire and shown as %. n indicates number of measured subjects. For calculation of p-value MC Nemar Bowker test was used. *Significant difference at p-value <0.05. V1 visit 1, V2 visit 2.

Figure 13: Smart Diet questions that changed from V1 to V3. a) Vegetable intake b) Low fibre bread intake c) Fish for dinner d) Meat as cold cuts e) Type of cheese. Data was collected from the Smart Diet questionnaire and shown as %. n indicates number of measured subjects. For calculation of p-value MC Nemar Bowker test was used. *Significant difference at p-value <0.05. V1 visit 1, V3 visit 3.
Lifestyle factors
Number of persons who smoked was reduced 32.0% during the study, however not the number of cigarettes smoked (table 14). Very small changes were seen in alcohol consumption and physical activity level (data not shown), and the frequency distributions were close to identical as for V3 (figure 9).

Table 14. Comparison of smoking status at V1 and V2, and V1 and V3.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>n (%)</th>
<th>n (%)</th>
<th>%-change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1</td>
<td>206</td>
<td>45 (21.8)</td>
<td>43 (19.9)</td>
<td>-1.9%</td>
<td>0.688</td>
</tr>
<tr>
<td>V2</td>
<td>112</td>
<td>41 (19.6)</td>
<td>43 (19.1)</td>
<td>-1.4%</td>
<td>0.581</td>
</tr>
<tr>
<td>Party smoker</td>
<td>22</td>
<td>9 (4.2)</td>
<td>10 (4.6)</td>
<td>11.1%</td>
<td>0.696</td>
</tr>
<tr>
<td>V1</td>
<td>216</td>
<td>47 (21.8)</td>
<td>32 (14.8)</td>
<td>-32.0%</td>
<td>0.003*</td>
</tr>
<tr>
<td>V3</td>
<td>116</td>
<td>43 (19.2)</td>
<td>29 (13.7)</td>
<td>-31.4%</td>
<td>0.010*</td>
</tr>
<tr>
<td>Smoking, number of cigarettes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>41</td>
<td>9 (4.2)</td>
<td>9 (4.2)</td>
<td>-</td>
<td>0.255</td>
</tr>
<tr>
<td>6-10</td>
<td>41</td>
<td>14 (6.5)</td>
<td>11 (5.1)</td>
<td>-21.4%</td>
<td>0.034*</td>
</tr>
<tr>
<td>≥11</td>
<td>41</td>
<td>9 (4.2)</td>
<td>8 (3.7)</td>
<td>-11.1%</td>
<td>0.116</td>
</tr>
<tr>
<td>Party smoker</td>
<td>41</td>
<td>9 (4.2)</td>
<td>13 (6.0)</td>
<td>44.0%</td>
<td>0.001*</td>
</tr>
<tr>
<td>V1</td>
<td>216</td>
<td>47 (21.8)</td>
<td>32 (14.8)</td>
<td>-32.0%</td>
<td>0.003*</td>
</tr>
<tr>
<td>V3</td>
<td>116</td>
<td>43 (19.2)</td>
<td>29 (13.7)</td>
<td>-31.4%</td>
<td>0.010*</td>
</tr>
</tbody>
</table>

Data are given as number (%).
*Indicates total number of measured subjects.

For calculation of p-values McNemar Bowker’s Test was used. *Significant change at p<0.005
V1 visit 1, V2 visit 2, V3 visit 3

4.2.4 Patients belief and preferences about lifestyle and treatment
The results from the patient’s preference’s schema are summarized in figure 14. Importantly, many patients wanted low cholesterol and thought that diet was as important as medicine.
4.3 Comparison between those with and without CVD

4.3.1 Clinical characterization, anthropometry and metabolic syndrome.

Forty-one patients suffered from CVD at V1, but this increased to 63 patients at V3. (figure 15). The CVD group included slightly more men, and were approximately ten years older when they first measured high cholesterol level, started medication, had their first consultation at the LC and at the end of the study at V3 (table 15). Comparisons of comorbidities and anthropometry of the patients with and without CVD at V3, are summarized in table 16 and 17. Further the patients with CVD used more antihypertensive medication, 73.0% vs 10.5%, and they had a higher percentage of MetS, compared to the patients without CVD (table 16).

Figure 17. Development of CV events from V1 to V3.

n indicates number of subjects. V1 visit 1, V3 visit 3, CVD cardiovascular disease, CV cardiovascular.

Table 15. Comparison of age between the patients with and without CVD at V3.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>CVD, n=63</th>
<th>No CVD, n=153</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First measured TC</td>
<td>61</td>
<td>150</td>
<td>9.8 (6.3, 13.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>First visit to LC</td>
<td>63</td>
<td>153</td>
<td>14.2 (10.8, 18.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Single medication</td>
<td>63</td>
<td>143</td>
<td>9.7 (6.6, 12.7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Double medication</td>
<td>57</td>
<td>119</td>
<td>8.8 (5.5, 12.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Triple medication</td>
<td>33</td>
<td>32</td>
<td>8.0 (3.3, 12.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>V3</td>
<td>63</td>
<td>153</td>
<td>12.2 (9.2, 15.1)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

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

*Indicates number of subjects analysed.

Age for medication is calculated from the starting date of the LLM, including statin, Ezetimibe, colesevelam, high dose omega-3, Niaspan, hypocol and PCSK9-inhibitor that was continued until visit 3. Change in dose or strength was not taken to consideration. A break for over 6 months was regarded as a discontinuation.

CVD cardiovascular disease, V3 visit 3. TC total cholesterol, LC the lipid clinic, CI confidence interval, LLM lipid lowering medications, PCSK9 proprotein subtilisin/kexin type 9- inhibitor

For calculation of p-value independent t-test and was used. *Significantly different at p-value<0.05
Table 16. Comparison of comorbidities of the patients with and without CVD at V3.

<table>
<thead>
<tr>
<th></th>
<th>CVD, n=63</th>
<th>No CVD, n=153</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(^a)</td>
<td>n (%)</td>
<td>n(^a)</td>
</tr>
<tr>
<td>Sex</td>
<td>216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (63.5)</td>
<td>76 (49.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23 (36.5)</td>
<td>77 (50.3)</td>
<td></td>
</tr>
<tr>
<td>Abdominal obesity(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>36</td>
<td>17 (47.2)</td>
<td>70</td>
</tr>
<tr>
<td>Women</td>
<td>19</td>
<td>13 (68.4)</td>
<td>62</td>
</tr>
<tr>
<td>Metabolic syndrome(^c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men(^1)</td>
<td>39</td>
<td>22 (56.4)</td>
<td>75</td>
</tr>
<tr>
<td>Women</td>
<td>21</td>
<td>10 (47.6)</td>
<td>75</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>63</td>
<td>46 (73.0)</td>
<td>153</td>
</tr>
<tr>
<td>Glucose lowering medications</td>
<td>63</td>
<td>10 (6.3)</td>
<td>153</td>
</tr>
</tbody>
</table>

Data are given as mean (95% CI) or number(%).
\(^a\)Indicates total number of measured people.
\(^b\)Abdominal obesity is defined as >102 cm for men and >88 cm for women.
\(^c\)The patient meet the criteria defined in NCEP ATP III or IDF or both. (35, 80)
For calculation of p-value Chi-square test was used and Fischer’s exact. *Significantly difference p<0.005
\(^1\)Significant higher prevalence for those with CVD when comparing all men p=0.001, and separating for those >55 years p-value=0.049 and those <55 years p=0.010.
CVD cardiovascular disease, V3 visit 3, CI confidence interval, NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III, IDF International Diabetes Federation.

Table 17. Comparison of anthropometric data of the patients with and without CVD at V3.

<table>
<thead>
<tr>
<th></th>
<th>CVD, n=63</th>
<th>No CVD, n=153</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(^a)</td>
<td>Mean (95% CI)</td>
<td>n(^a)</td>
</tr>
<tr>
<td>WC, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>36</td>
<td>103.7 (99.2, 110.2)</td>
<td>70</td>
</tr>
<tr>
<td>Women</td>
<td>19</td>
<td>93.7 (88.5, 99.0)</td>
<td>62</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>40</td>
<td>28.7 (26.7, 30.7)</td>
<td>76</td>
</tr>
<tr>
<td>Women</td>
<td>23</td>
<td>26.9 (25.3, 28.5)</td>
<td>77</td>
</tr>
</tbody>
</table>

Data are given as mean (95% CI) or number(%).
\(^a\)Indicates total number of measured people.
For calculation of p-value independent t-test was used. *Significantly different at p=0.005.
CVD cardiovascular disease, V3 visit 3, WC waist circumference, CI confidence interval, cm centimetres, BMI body mass index, kg/m\(^2\) kilogram per square meter.

4.3.2 Lipid lowering medications
The CVD group were more intense treated with both more LLM and higher intensity of statin treatment at V3, as seen in figure 16. However they started at a higher age with single, double and triple LLM (table 16).
Figure 16. Comparison of the patients with and without CVD at V3 with regard to A) Number of LLM used B) Statin therapy intensity and the use of PCSK9-inhibitors.

Data are given as percent (%) and n indicates number of analysed subjects.

1High intensity statin therapy: atorvastatin 40-80 mg or rosuvastatin 20-40 mg.

2Moderate 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 pitavastatin 2-4 mg.

3Repatha 140mg, Praluent 75mg or Praluent 150mg

p-value was calculated with Chi-square test. *Significant difference at p-value<0.05

CVD cardiovascular disease, PCSK9-inhibitor proprotein subtilisin/kexin type 9-inhibitor. LLM lipid-lowering medicine, mg milligrams

4.3.3 Blood parameters

Figure 17 compare the ages and the associated TC levels at important time stages, for those with and without CVD. The rest of the blood lipids are compared in table 18.

Figure 17 Comparison of patients with and without CVD at V3 with regard to a) Their age at important time stages b) TC at important time stages

Data are shown as mean with 95% CI error bars. n indicates number of analysed subjects.

For all time stages there were 216 attending subjects except at V2 where there were 206.

Missing values for both table 17a and 17b:
- CVD: untreated n= 2, first time at LC n= 3, V1 n= 0, V2 n= 2 and V3 n= 0
- nonCVD: untreated n= 3, first time at LC n=, V1 n= 1, V2 n= 9 and V3 n= 0

P-values was calculated using independent t-test. *Significant difference p<0.05.

TC total cholesterol, LC the lipid clinic, V1 visit 1, V2 visit 2, V3 visit 3, CVD cardiovascular disease, mmol/L millimoles per liter
Table 18. Comparison of blood parameters of patients with and without CVD at V3.

<table>
<thead>
<tr>
<th></th>
<th>CVD, n=64</th>
<th>No CVD, n=152</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(^a)</td>
<td>Mean (95% CI)</td>
<td>n(^a)</td>
</tr>
<tr>
<td>Untreated TC, mmol/L</td>
<td>61</td>
<td>11.3 (10.7, 11.9)</td>
<td>150</td>
</tr>
<tr>
<td>Untreated LDL, mmol/L</td>
<td>22</td>
<td>9.2 (8.0, 10.4)</td>
<td>67</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>63</td>
<td>4.8 (4.5, 5.2)</td>
<td>153</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>63</td>
<td>1.4 (1.3, 1.5)</td>
<td>153</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>63</td>
<td>2.8 (2.5, 3.1)</td>
<td>153</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>63</td>
<td>1.3 (1.2, 1.4)</td>
<td>152</td>
</tr>
<tr>
<td>ApoB/ApoA1 ratio</td>
<td>60</td>
<td>0.7 (0.7, 0.8)</td>
<td>147</td>
</tr>
</tbody>
</table>

Data are given as mean (95% CI) with the exception of blood glucose and HbA1c which are given as median with 25\(^{th}\)-75\(^{th}\) percentile.

\(^a\)Indicates total number of measured people.

For calculation of p-value independent t-test and was used, with the exception of blood glucose and HbA1 where Man Whitney sign rank test was used. \(^*\)Significant difference at p-value <0.05

CVD, n=64; No CVD, n=152

4.3.4 Dietary factors

The CVD group scored a mean (95% CI)) 37.1p (36.2, 37.9) of a maximum 45p which were significantly (p=0.021) lower than those without CVD with a mean 35.8p (35.2, 36.4). (Data not shown) There were no significant differences in the main Smart Diet categories (figure 18). Figure 19 shows the Smart Diet questions that were significantly different between these two groups. The rest of the Smart Diet questions were not significant different (data not shown).

Figure 18. Comparison of distribution of Smart Diet categories of patients with and without CVD at V3.

\(^a\)Indicates number of analysed subjects.

\(^b\)\(\geq 38p\), \(\geq 31p\) or \(\geq 36p\) in the 2003, 2007 or 2009- version of Smart Diet respectively. 2003-version was preferred.

\(^c\)\(30-37p\), \(25-30p\) or \(28-36p\) in the 2003-, 2007- or 2009- version of Smart Diet respectively. 2003-version was preferred.

\(^d\)\(\leq 29p\), \(\leq 24p\) or \(\leq 27p\) in the 2003, 2007 or 2009- version of Smart Diet respectively. 2003-version was preferred.

For comparison of p-value Chi-square test was used. \(^*\)Significant change at p<0.05.
4.3.5. Lifestyle factors
There were no significantly differences in the lifestyle factors between the two groups (table 18). The majority had over three physical activity sessions a week, drank 1-7 units of alcohol, and did not currently smoke.

Table 19. Comparison of lifestyle factors of the patient with and without CVD at V3.

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>CVD</th>
<th>No CVD</th>
<th>% Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity a week*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>53 (5.6)</td>
<td>139</td>
<td>5.1</td>
<td>0.390</td>
</tr>
<tr>
<td>&lt;1</td>
<td>8 (14.8)</td>
<td>22 (16.7)</td>
<td>-1.9</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>18 (33.3)</td>
<td>54 (40.9)</td>
<td>-7.6</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>25 (46.3)</td>
<td>54 (40.9)</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Alcohol, units&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>62 (17.7)</td>
<td>152</td>
<td>6.5</td>
<td>0.390</td>
</tr>
<tr>
<td>&lt;1</td>
<td>17 (27.4)</td>
<td>36 (23.7)</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>1-7</td>
<td>28 (45.2)</td>
<td>86 (56.6)</td>
<td>-11.4</td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>6 (9.7)</td>
<td>13 (8.6)</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>63 9 (14.3)</td>
<td>153 23 (15.0)</td>
<td>-0.7</td>
<td>0.888</td>
</tr>
<tr>
<td>Former smokers</td>
<td>63 30 (47.6)</td>
<td>153 54 (35.3)</td>
<td>12.3</td>
<td>0.091</td>
</tr>
</tbody>
</table>

Data are given as number (%).
*Indicates number of analysed subjects.
*One session was over 30 minutes.
<sup>c</sup> Categorized as number of units consumed weekly. A unit is defined as 125ml wine, 330ml beer or 4 cl spirits.
For calculation of p-value Fischer’s Exact and Chi-Square test was used. *Significant difference at p<0.05.
CVD cardiovascular disease
4.4 Cardiovascular events and death
Mean (95% CI) average age at first CV event was 46.6 years (43.9, 49.2) (data not shown). Both previous CV events, and those that occurred during the study are summarized in table 20. 43 patients were also described as having AP, however frequency, duration, medication and documentation was not fully recorded in every patient. During the study eight men and four women died. The median age of death was 64.8 years, the youngest died 38.3 years old and the oldest 76.1 years. Data of the patients who died are not included in any of the other analyses. However, their medical records reviled that half of them had CVD or died from CVD. Furthermore, six smoked daily, and four of them had suffered from CVD. Median smoking time was 34.5 years, the shortest time was 18 years and maximum was 57 years. They had smoked in average 10 cigarettes a day (data not shown).

Table 20. Type and frequency of CV events before V3.

<table>
<thead>
<tr>
<th>Number of patients with CVD at V3, n=63</th>
<th>n</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MI’s</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Number PCI’s</td>
<td>29</td>
<td>48</td>
</tr>
<tr>
<td>Number of carotid stenosis</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>CABG</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Data are given as mean (95% CI) or number.
CVD cardiovascular disease, V3 visit 3, CV cardiovascular, CI confidence interval, MI myocardial infarction, PCI Percutaneous coronary intervention, CABG Coronary artery bypass graft.
5 Discussion
This a prospective study that examines what patients with FH can achieve by an intensive treatment in a specialized LC in a real life setting. The patients were followed in a period of eight to ten years, from 2006 to 2017.

5.1 Subjects and methods
The thesis is a continuation of two previous, (156, 165) with an increased number of FH patients analysed and discussed.

5.1.1 Participants

Living with FH
The participants are middle-aged. They were aware of their FH diagnosis, and medically treated for it, before entering the study. This has made them learn to live with FH, and made them aware of the consequences of FH. Close to one out of three have experienced a CV event, at a highly premature mean age of 46.6 years. Many of the patients have a close family member who have CVD, or even died as a cause of it. A recent study (17) in Norway found that CVD was the cause of death in 50% of the FH patients, and furthermore 69% experienced one or more MI before the time of death. Given this, the motivation to participate to help in a scientific project is huge among those with FH. By participating they can have an active role in their own healthcare situation with a close follow-up by health care professionals, and the results can help improve treatment guidelines for the next generation.

Participation rate
In this study the participation rate for V1 was impressively 89.3% of those invited and met the inclusion criteria’s. Of those who were still alive, and met the inclusion criteria’s at V3, 63.2% completed the study. The invitation of the participants was effective and cost efficient, since all the participants were invited at their scheduled follow-up appointment at the LC. Both the fact that their own doctor at the LC, a person the patient knows and who know their medical history recruited them, and that many previously had participated in studies at the LC, were advantageous and may have contributed to the high participation rate. V2 and V3 for each participant were done at a time when they were intended to have their routine consultation at the LC, making it easier to accept the invitation to the study, since they were coming to the LC anyways. The only drawback was that the appointment would take more time than usual, since there was both a doctor consultation and an interview with the master student at V3, on top of answering questions and schemas.
There is a possibility that non-response bias occurred. Those individual who refused to participate, either at start or fulfilling the whole follow-up period, may have been systematically different from those who accepted to participate. (166) “The healthy volunteer effect” is a well-known phenomenon, when healthy individual are more likely to participate in a study. In the examination of the participation in the Rotterdam Study (167) they reported that a 1% increase in coronary risk yielded an approximately 3% lower probability of participating, when the association between participating in the third examination, all cause mortality and coronary risk were analysed. Further findings were that those who were categorized as “high risk” were least likely to participate. In our study there were various reasons why not the remaining 141 participants, did not participate at V3. The largest group consisted of 110 patients who were not patients at the LC anymore. Data regarding those were not gathered, but they may have had higher cholesterol levels and poorer adherence to medical treatment and diet recommendations if they have not consulted other specialists in dyslipidaemia.

**Diagnosis**
92% of the participants have genetic verified FH. That strengthens the results we find in this study because they are reliable in sense that it describes people with a genetic cause to high cholesterol values, in contrast to those with just a phenotypic FH, where only the most severe cases are detected, and the cause of high cholesterol can be many. (15) Furthermore contributing factors to increased CV risk, other than the genetic component of elevated cholesterol levels, and possible protective factors of premature CV events can be analysed.

**Patient history at the LC**
The participants had been patients at the LC for approximately 10 years, in average, before the study started. During this time they had regular follow-up consultations at the LC with a doctor, and if needed also consultations with a clinical nutritionist. Thus, we expected the patients to be well informed and in some cases optimal treated even before entering in to the study, so the potential for further improvements in diet and lipid values during the study period were somewhat reduced. Another disadvantage with frequent consultations with the doctors and clinical nutritionists, who both uses Smart Diet questionaries’ as base for a discussion on healthy dietary habits, is that the patient have a good understanding of what dietary choices are cardio protective healthy, and which answers in the Smart Diet that gives the best score. This opens for subconscious biasing in the diet and lifestyle assessment, towards answering what is perceived to be appropriate. (168, 169) Undesirable lifestyle factors known to increase CV risk, such as a sedentary lifestyle, smoking and eating high
amount of saturated fat, may have been underreported. The opposite may have occurred with factors contributing to good health, such as high consumption of fish, fruit and vegetables, and high level of physical activity, which may have been over-reported. As an effort to reduce this bias, the participants answered the Smart Diet by themselves before the consultations.

The study was initially a quality study of the treatment given by the LC, and therefore the patients without LLM at V1 were excluded from study. However at V3 those patients without LLM were included and analysed, as they are a normal variation of the treatment state.

5.1.2 Study design and implementation of the study

The LC in Oslo
The study was conducted at the LC in Oslo, established in 1984. It is a leading lipid clinic in Norway, treating children and adults with dyslipidaemias from the whole country. Hence, it is the perfect place in Norway to reach the target group, patients with FH. The LC have a two-folded task as an out-patient clinic, offering consultations by doctors and clinical nutritionists, and running scientific based research on both children and adults. They have conducted multiple studies over the years, and have large routine in running scientific projects, which is an advantage when the cohort is followed for a long period of time, and is dependent on help from many persons to succeed.

Advantages with long-term follow up
The advantage of a long-term follow-up study, is that it provides information about changes in the disease and lifestyle over time, in addition to the cross-sectional picture. In addition to collecting biochemical parameters and other objective findings, the study obtained the participant’s preferences about medication, diet and cholesterol levels weighted against the adverse effects of LLM. Few other studies have investigated these problems. Another advantage for the patients, who entered the study, was a probable health benefit effect.

Bias
A weaken with the study, is that in a few cases another doctor than the principal investigator met the patients and further that three different master students were involved at different times. Information bias may have occurred. However, all doctors used the same case report forms and were instructed use similar procedures. Since this was part of a regular patient consultation at the LC, the measurements and questions were not identical measured and asked. WC, measured by a measuring tape and not a calibrated machine, is difficult to measure identically, and the recommended locations for WC measurements vary. (35, 170, 171) The WC was analysed in different ways as a mean, abdominal obesity or not, and used
both the IDF and the NCEP ATP III definitions to diagnose MetS, as an effort to keep the measurement errors at a minimum.

As for the questions during the consultations, observer expectation bias may have occurred, especially in the evaluation of adverse effects where no measurements or biochemical data were used. The doctor’s own expert opinion and the dialog with the patient, formed the base for the doctors differentiation of the adverse events to certain, possible or probable. Emphasising on different questions or gesturing may have taken place. (166) The doctor’s prior insight of the patient’s history may have influenced the structure and sound of the questions. (172) The same doctor had almost all of the consultations at V3, and the patients filled out the patient preference’s form and the Smart Diet by them selves before the consultation. This was an effort to reduce the information bias. However for each part of V3 there were a different master student, and even with close communication between them, information bias cannot be rule out.

**Specific challenging blood parameters**

The timespan and frequency of the measured Lp(a) varied immensely between the subjects. Given this, in addition to the aspect that the reference area for Lp(a) is strongly dependent on the assay method used, which has changed over the decades, and is different for each laboratory, it is difficult to draw strong conclusions from these data. Furthermore, a comparison has to be made comparing the values for the same laboratories, which was not possible in this study. (Medical director Eva C. Langsjøen at Fürst laboratory, personal contact). Missing comparable data on Lp(a) values is a limitation, since other studies have found Lp(a) to be higher among FH-patients compared to the general population, and higher among FH-patients with CVD versus those without CVD. (61, 62, 173, 174)

16% of the patients measured a CRP level over 3mg/L at V3, which is suggested to correspond a high CRP related risk of CVD. (101) The strength of these findings is debatable, given the fact that a single measurement shows a huge technical and biological variation, and gives little information. (161, 175) Furthermore CRP is especially susceptible to confounding, since multiple CV risk factors’ such as smoking, hypertension, obesity and physical inactivity, independently can raise the CRP plasma levels. (103)

**5.1.3 Data processing**

As described in the section 3.2.1, the data was quality controlled to minimize accidental bias in the plotting process, both before and during the analysis. Random samples and extreme
values were double and triple checked. As the variables checked were in most part in accordance to each other, inter-variability, both differential and non-differential, was avoided to the greatest extent. Despite this, the possibility of errors not being discovered, or that the patients intentionally or unintentionally gave given erroneous information, cannot be ruled out.

With increased number of patients analysed, the conclusions and results from the previous two master theses have been modified and strengthened. (156, 165) In the present thesis the topic of interested were the current state at V3, and the changes over time for all the variables from the short period from V1 to V2 and the whole study period over eight to ten years, until V3. Further we studied if there were any differences in those with CVD at V3 compared to those who did not. Most of the variables were normal distributed and analysed with parametric tests. Further, calculated frequencies, cross tabulations and explorative analyses were used. Correlation and regression analyses for evaluation of different variables influence on CV risk would have been quite interesting, but was regarded as too much in additional to the results already summarized in this master thesis.

There were missing data in several analyses, and they are classified as item non-response. To avoid missing information paired exclusions in the analysis were used. Concerning the blood parameters, LLM and the adverse effects of medications, there were no or only a few missing data. But for untreated LDL-C there was few to analyse. The blood parameters with the highest number of missing values were BP, blood glucose and HbA1c. As for the anthropometric data the height at V3 was used to calculate all BMI, and weights were in some cases only reported by the patient and not measured. There were very few WC measured overall. WC is fundamental for diagnosing MetS when using the IDF criteria’s and the NCEP ATP III criteria’s. (35, 171)

In the Smart Diet questionnaires, there were quite a number of missing data at either V1 or V2, both concerning diet and the intensity of physical activity. All missing data was regarded as non-response. Missing values were partly due to the fact that some of the patients forgot to tick off all of the Smart Diet questions, did not finish the questionnaire prior to the consultation, took the questionnaire with them home, or answered the 2007 version instead of the 2003 version. All were mistakes that could have been avoided with closer attention during consultations. This may imply that there is a need for more consultations with clinical
nutritionists who have their focus on diet and physical activity. The strength of the results of the comparisons of change in Smart Diet score, categories and questions were diminished because of the high portion of missing values.

The presence of many missing values in the study reduces the number and the statistical power to detect differences, and this weaken our results. This was especially evident when comparing the different visits using paired analytic tests. These tests require values for each individual at each time. The amount of missing data may reflect the fact that not the same personnel collected all the data. Although the missing data may have influenced the results to some degree, the clinical findings were usually in the normal range, and corresponded to the values found in the general population and other studies.

5.2 Results

5.2.1 Present state at V3 and the changes over eight to ten years

Age at diagnosis
FH is underdiagnosed. (15) With lifelong exposure to high levels of LDL-C, the FH patients have an increased risk of premature CVD, thus an early diagnosis and treatment is essential. (15, 20) In this thesis we reported an average age of 26.8 years as first measured high TC, and first appointment to the LC at an average age of 33.3 years. In between these two periods they were genetically diagnosed with FH (the exact date is not present in our data). This is late and not desirable, since the severity of atherosclerosis is proportional to the extent and duration of elevated plasma LDL-C levels. (18) The patients in our study were ten years younger when diagnosed compared to the FH patients in the Cascade Screening for Awareness and Detection (CASCADE) FH Registry in the USA, where only 22% were diagnosed before 30 years of age. (176)

Partly the reason for late discovery of FH, may be lack of awareness of the disease among the general practitioners that have to referrer these patients to the LC. The patients themselves have the responsibility to alarm their close relatives that they carry a genetic disease, since health care providers are not allowed to do so in Norway. (177, 178) The universal recommendation for screening lipids, at the age of 20 came in 1988, when this FH population on average were in their mid-twenties. (179) Molecular genetic testing for FH was, however not routinely available in Norway before 1998, when this FH population were in their early thirties. (180) Prior to this FH was diagnosed clinically, and only the phenotypically most severe cases were detected probably, leading to many undetected cases. (28) One study (180)
in Norway showed that only 50% FH patients were identified when using clinical diagnostic
criteria compared to genetic testing. Today a maximal cost-effective cascade screening is
recommended using a combination of plasma lipid profiles and genetic testing. (15)

**Lipid-lowering medication used and starting time**

Over 90% of the patients used statin treatment at the end of the study. The vast majority used
high intensity therapy, and some used moderate intensity therapy. This is according to the
guidelines, since low potency statins, generally are inadequate in FH. (15) Low intensity
therapy could have been preferred because of adverse effects, where the optimal treatment
could not be endured, or because they had a mild FH phenotype or their cholesterol values
responded well with a healthy diet and physical activity, so a relatively low intensity statin
treatment was sufficient. With the exceptions of a study among FH patients in the Netherlands
(181), this is a higher percentage of statin users among FH patients, than shown in studies
from France (182), USA (176), Spain (183) and England (184). All the patients who reached
their LDL-treatment goals at V3, used statin treatment. Around 50% used statin in a
combination with Ezetimibe as a double medication, the same level as for the FH patients in
the Netherlands. But also here, Norway and the Netherlands have higher frequencies than
reported from France, USA and Spain. (176, 181-183) 30% used three or more LLM in our
study, indicating that the participants were an intensively treated patient group.

When comparing the sexes, the men were treated more intensively. Double treatment was
almost similar in men and women, but 48.0% of the men with double medication increased to
triple versus only 21.6% of the women. Further only men increased to quadruple medication.
This was in the very early start of the use of PCSK9-inhibitors, and probably this finding are
related to the very high CV risk seen in some of the men in the TTT-FH study. A study (185)
showed that even though women had a worse CV risk profile than men, they had less
widespread CHD. In our study more than 60% of those with CVD were men, in other studies,
such as the INTERHEART study and the SAFEHEART study, and in the risk score
evaluation from Framingham and the Montreal-FH-SCORE, the male sex has also higher
likelihood of CVD compared to women at the same age. (31, 32, 173, 186)

Furthermore, the men started on medication in average at an age of 31.9 years, this was six
years younger than the women who started as late as 37.8 years of age. Life expectancy for
FH patients was reported to be approximately 60 years in Norway, suggesting that these
women have lived two-thirds of their lives before starting the adequate medical treatment for
FH patients. (187) Almost three decades later than recommended. (28, 129) In the CASCADE FH-registry the average age, not distinguished between the sexes, was even higher at median age of 39 years, and only 16.6% started LLM before 30 years of age. (176) This is a concerning late start because the CVD risk increases progressively with age. (31, 35, 186) If the first measured TC level at 10 mmol/L, have been present for three to four decades without treatment, this is critical for the present and further development of CVD, since the severity of atherosclerosis is proportional to the extent and duration of elevated plasma LDL-C levels. (18) The sex differences in age were only significant at the start of single medication.

The halt in LLM in periods of pregnancy and lactation
A note to mention is that the periods of conception, pregnancy and lactating, interrupts the continued medication among the women because LLM, including statins and Ezetimibe, are not recommended during these periods. (35, 141, 167) There has been inconclusive information about the use of LLM in pregnancy, so the fear of possible teratogen effects is present. (141) Physiological changes in lipoprotein metabolism, including TC and LDL-C increment up to 50% peaking at the second trimester, higher HDL-C throughout the period and TG levels doubled, occur in all normal pregnancies. (188, 189) As non-pregnant levels are severely elevated in FH women, especially if they are medically untreated, the absolute magnitude of these changes is considerably higher for them. (190)

A women well treated medically since childhood, who have never smoked, is physical active and have a cardio protective diet, are better prepared for the child bearing years. However this was not the case for most of the women in this study. 44% of the women did not start medication until after childbirth. If this was a deliberate choice or not, is unknown in our data. But the average age for women at first measured high TC was 27.9 years, the exact averaged aged for a mother delivering her first-born baby the same year this study started. (191) 16% of the women did not know their TC level after passing 40 years. Waiting with LLM until after the childbearing years does not only affect themselves. A recent study (192) shows that it also affects their children. Women with elevated cholesterol in early pregnancy, was reported to have offspring with higher LDL-C at 6 to 13 years. The lifestyle is even more important if a patient is not medically treated. The average Smart Diet score obtained in V3, which had increased during ten years of follow-up, was not optimal. There were even some smokers, many former smokers, and only half of the subjects did the recommended level of physical activity, which is not an optimal start for pregnancy.
Only 22 women used LLM before their pregnancy. In average they used LLM only for 7.9 years prior to the pregnancy, and the period without LLM lasted in average 4.2 years. The results are based on too few patients to conclude that the time period without LLM, due to pregnancy and lactating, is representative for all FH-women. But still, the length of the period fits well with the fact that the average woman in Norway delivered 1.7 babies in 2016. If a period without LLM due to pregnancy and lactating last in average 4.2 years, the period is not that long. The damaged that it could possibly cause is minimized with early detection, diagnosis and treatment. Because then the women would have the opportunity to be well treated, and incorporate healthy dietary and lifestyle habits before their childbearing years.

Adverse effects
One out of three had adverse effects from statin treatment, almost the same frequency was reported with colesevelam. As discussed earlier, there is some possibility of information bias in the data collection, and these data are collected as part of a subjective patient experience, and no direct measurements are done. On the other side, the long term follow-up and repeated discussions and rechallenges of medication and doses, makes a good basis for evaluating the side-effects as described. Unfortunately data on adverse effect from the different LLM were only gathered at V3, so a change during the study was not detectable.

Muscular complains and gastrointestinal problems were the main reported adverse effects reported from statins. Muscular complains were also reported by a cross section survey, answered by clinicians all over the world treating FH, to be the most frequent adverse effect. (137) This is confirmed in a consensus statement from the EAS. They reported this as one of the principal reasons for statin non-adherence and/or discontinuation. (193) The cross sectional survey further reported that an average of 6% had confirmed adverse effects by a set of criteria´s much alike to ours. (137) This is consistent with our study where 6.5% were defined as having definite side effects, the rest were categorized as probable or possible, 17.5% and 8.5% respectively. The high percentage of patients in the groups probable and possible may be somewhat influenced by the fact that muscular intolerance to statin has become a well-known phenomenon among users. A simple Google search “statin side effects” made 443 000 hits, “statin muscle pain” made 566 000 hits (as of October 2017). This might have shape the public opinion about adverse effects of statins. The biological mechanisms of statin induced muscle pains are not clear. A meta-analysis (194) of over 125 000 patients, suggests that the rate of drug discontinuation and myopathy was not significantly different between statin- and placebo-treated patients in a randomize control trial. A point well made is
that statins do cause a rare side-effect known as myositis, defined as muscle symptoms in associations with a substantially elevated serum creatin kinase concentration. (193, 195) This was however not reported or found in any of the patients at V3.

Resins, like colesevelam was not commonly used compared to statins, 25.5% used colesevelam versus 92.6% who used statin. Adherence is often an issue due to poor palatability and increased occurrence of gastro intestinal (GI) adverse effect. (30, 196). Of the patients who used colesevelam one out of three reported adverse effects and all, except one, reported it as GI problems. 25% of the adverse effects were defined as definite, four times higher percentage than the definite adverse effects of statin. Of the other LLM used at V3 there were only reported one or zero cases of adverse effect.

Patients without statin and/or lipid-lowering medications
Discontinuation of statin therapy by FH patients because of adverse effects increases the risk of CV morbidity and mortality, and this was the number one reason for those without statin in our study. A meta-analysis (197) of statin treated patients, showed that those adherent more than 80% of the time with their prescribed statin had a 15% lower risk of CVD than those less adherent.

Three women who off statins because they wanted to conceive a child or were lactating, and they were not analysed further. Even after taking out these three subjects, 69.2% and 62.5% without statins or without LLM at all, respectively, were women. This is also supported in the literature where women are reported to stop statin therapy because of side effects more often than men. (198, 199) Women were also less likely to use alternative LLM, (199)

As expected for genetically verified FH patients without statin treatment, the blood lipids were severely high with a median TC 9.5 mmol/L and LDL-C 6.6 mmol/L. The lowest values measured were 5.1 mmol/L and 6.6 mmol/ for TC and LDL, respectively. When taking out the five patients with LLM and looking at the patients completely without LLM, TC and LDL-C levels were, as expected, higher with a median value at 10.4 mmol/L and 7.2 mmol/L for TC and LDL-C, respectively. These levels are over four times higher than recommended LDL-C targets for primary prevention. (19) The ApoB/ApoA1 ratio at 1.2 for those without LLM, was almost twice the recommended target at <0.7. (48)
In addition to unfavourable blood values, some also had additional CV risk factors, including MetS, hypertension and CVD. Two out of three with CVD used Ezetimibe and PSCK9-inhibitor. These drugs, are recommended to use when statin causes adverse effects. (200) However PCSK9-inhibitors, with a LDL reduction capacity of up to 60-70%, have strict restrictions to whom can get the prescription. (145, 201) The median continued time off statins for the thirteen patients were 4.0 years. When taking in to the account the late onset of LLM, and one or more childbirths for women, the years without LLM are considerably, especially for women. On the positive side, half of the patients started a new statin treatment at V3.

**Blood parameters and LDL-treatment target**

After in average 20 years the patients have achieved a remarkable 50% reduction in TC and LDL-C from untreated values demonstrating very long time compliance and effects including a 10% decrease to 5.0 mmol/L during the study follow up. This is a greater reduction from untreated values than seen in other clinical lipid studies. (25, 176, 182, 202, 203) A reduction >50% in LDL-C is the initial aim for FH. (22, 129) Untreated LDL-C values were identified in approximately 40% of the patients. 76.4% of these patients achieved >50% reduction in LDL-C values at V3. This indicates that it is realistic for FH patients to reach the initial aim of a 50% reduction in out patient treatment. In the studies from the Netherlands, England and USA, this initial aim was achieved by 41-64%. (176, 181, 184) Though, in our patient population we had higher untreated values than the other lipid centres studies. Non-HDL was reduced to significant lower at V3 with a final level of 3.6 mmol/L. Even with this 14% reduction the levels are higher than the recommended. (204)

Only one out of five achieved the specific LDL-C target set by the EAS. (19) In primary prevention 30.2% achieved the goal and in secondary prevention it was achieved by 8.5%, 50% of them used PCSK9-inhibitor. So, combined LLM are needed to reach the target values. 35.9% of all the patients achieved <2.5 mmol/L in LDL-C at V3. This is in the upper ranges when comparing to the other FH lipid clinics in other countries, percentage of subjects with LDL-C <2.5 mmol/ varied from 3-30%. (176, 181-184)

In measurements there is a possibility of analytic and biological variance. Fürst laboratories reported that to be 2% and 8.4%, respectively, in LDL-C measurements. (205, 206) So, from a clinical perspective, close to target LDL-C values are very interesting. LDL-C levels no more than 15% higher than treatment target were counted as close to target values. 38.9% of
all subjects were at, or close to LDL-C target value at V3. In primary prevention close to 50% were at, or close to target LDL-value, and in secondary prevention one out of four were at, or close to LDL-C target value. This shows, that even though there are few patients who actually achieve the specific LDL-C target, this number is doubled if you include those who are very close to achieving it. When a patient is so close to achieving a target value, doctors may choose to be satisfied with this, and may therefore be more restricted to increase the medicine dose, or add more LLM. Increase medicine dose, or add more can be both more demanding for the patients, and induce more adverse effects. The cost for the patient is always being considered in comparison to the clinical importance of a slightly further reduction in LDL-C. If no changes regards to LLM are done, further improvement in diet and other lifestyle factors should be put in focus to, so treatment target can be achieved.

Even with significantly reduced levels of LDL-C, the CV risk can still be to high as there are other atherogenic components that are important in the atherosclerosis. ApoB, which are on the surface of all atherogenic lipoproteins, were significantly elevated at V3, and was increased 10% from V1. Recommended levels are <1 g/L and < 0.7 g/L for those in primary and secondary prevention, respectively. (19) This was not achieved, and the final average level was 1.1 g/L.

TG was also significantly higher at V3, at a final level of 1.2 mmol/L. This 20% increase, reflects an increase in TG-rich remnant lipoproteins. Some of these are atherogenic and involved in atherosclerosis, whereas others are not. (207) Over twenty percent intra-individual variation of TG has been reported, and this is caused to some extent by analytical variations but also by environmental factors such as diet and physical activity. (19) This increase in both TG and ApoB concomitant with lower LDL-C concentration, could imply that a more atherogenic profile, with increased levels of small dense LDL particles, may have developed during the study-period. (19, 38, 207). The increase in weight and prevalence of MetS could be contributing factors. However, the 14.3% decrease in non-HDL suggest otherwise. Same with the 7% increase in ApoA1, which is strongly associated with HDL-C and have invers association with the incidence of CVD. (42, 43) With increased levels in ApoB and ApoA1, the ratio of ApoB/ApoA1 stayed the same, at 0.7. This reflects that the balance between the atherogenic and the anti-atherogenic particles have stayed the same during the study. The level is in the upper range for those with high risk of CVD, as FH patients are. (38, 48) Conclusions from the AMORIS study, describes this ratio to be the single best lipid-related
risk variable, after adjustment for age, compared with the other conventional lipids and lipid ratios. (40, 48)

**Metabolic profile risk**

Weight, BMI and WC all increased significantly during the study. At V2 the subjects had increased their weight by 1.6 kg, and at V3 this was doubled. A weight gain of around 0.5 kg a year, for men and for women is, especially among the middle aged, is observed in other studies as well. (208, 209) But weight gain still increases the risk of chronic diseases, especially CVD and DMT2, as seen in the Framingham study. (210) There was no improvement in physical activity level observed in our data, but this parameter was not good enough to separate sharply the true length and intensity, and differentiate between the individuals. The length and intensity of the physical activity level may have somewhat decreased during the study. Regardless of that, the general physical activity level was low during the study, and this may have contributed to the increased weight. Probably, the weight gain is also caused by an increased energy intake. Even though the Smart Diet showed improvement in the cardio protective score, it is not validated to estimate energy intake. (163) An unbalanced energy intake and output will increase weight, and this again will lead to increased risk of MetS. (80) Close to one third of both men and women had MetS at V3, both based on the NCEP ATP III or IDF criteria’s. (35, 80) This is a worrisome high prevalence, especially since MetS is associated with up to 2-fold increased risk of CVD, MI, stroke and CVD mortality. (79, 211)

There were too many missing data to optimally compare the development in prevalence of MetS during the study, but in average most of the parameters significantly increased. The average WC was equivalent to abdominal obesity for women, and close to that for men, when cut off values from NCEP ATP III were used. (35) Increased WC is an unhealthy development toward MetS, and actions should be taken to reduce, or at least to prevent further increase. Fasting blood glucose and HbA1c increased with 10.0% and 5.5%, respectively, from V1 to V3. With mean (95% CI) fasting blood glucose of 5.6 mmol/L (5.3, 5.8) and HbA1c at 5.7% (5.6, 5.8), the average FH-patient in this study was in the range of pre-diabetic stage when using American Diabetes Association Criteria’s (212) 9.7% of the patients used diabetic medication.

Without a control group, it is difficult to identify why so many developed reduced glucose tolerance and insulin resistance. However both the LLM and the increased visceral fat may
have influenced. Statins has been shown to impair insulin sensitivity and secretion, thereby increase the risk of DM. 9-12% increase has been seen in two meta-analysis (213, 214), and an even higher prevalence is seen in population-base studies. EAS do however not recommend discouragement of statins, since the absolute risk reduction of CVD in high-risk patients, like FH, outweighs the possible increase in incidence of DM. (19) Colesvelam on the other hand, has been associated with lowering HbA1c. (215) Increased visceral fat is highly associated with insulin resistance. (77) The measurements of WC have a lot of missing data in our study. They were also too uncertain measured for comparison. Further, WC cannot distinguish between visceral and subcutaneous abdominal fat. (30, 76) If a hip circumference had been taken, and the hip-waist ratio calculated, a better understanding of visceral to subcutaneous fat could have been made. The hip-waist ratio is also a much stronger predictor for MI, as seen in the INTERHEART study. (75)

TG and HDL, as previous discussed, are the two other blood parameters constituting the MetS. TG increased during the study, but the average values was still far from the metabolic cut off at ≥1.7 mmol/L. HDL increased from V1 to V2, but were back to the starting level at V3, and still on average above cut off levels for MetS. (35, 80) High BP is also a part of the MetS criteria. (81) 28.2% received antihypertensive treatment, and the average BP was at normal levels. Their BP was treated optimally.

Dietary and lifestyle factors
A more cardio-protective diet was achieved, documented by a significant increase in Smart Diet score, both in the short period from V1 to V2, and until V3. The average score was 36.2 p at V3, and that was in the upper range of the medium category with the cut of value for ≥38p for the highest category. A10% raise in the highest Smart Diet category was seen during the study, but still 60% was in the medium category. Less than 10% were in the lowest category at any visits during the study.

In general they had an overall good score in all the dairy questions, with the exceptions of cheese (see further discussion). They used mostly oils for cooking, but the Smart Diet questionnaire did not specify what kinds of oils they used. If the highly saturated palm- and coconut oils were used, that is not beneficial at all. These types of oils increase the cholesterol. Other vegetable oils, containing a lot of mono- and polyunsaturated fatty acids, have a much more beneficial effect of reducing cholesterol values. (148, 151) Further, they ate generally lean meat, and the fish consumption was at recommended level. (88, 150) Fruit
and vegetable intake could have been better, seen that 34% reported to eat ≤1 portion of fruit/berries/ juice a day, and 30% reported to eat ≤1 portion of vegetables a day. A collective score for this was not gathered, but based on the separate questions it looks like the majority were under recommended levels of fruit and vegetable intake a day. (88) Sweet spread and sugar-holding beverages were used in moderation, but 42% reported a candy/chocolate/biscuit etc. intake of 2-3 times a week. This is high, and may be over the recommended sugar intake of 10 E%. But, this is difficult to estimate since the Smart Diet, does only score based on frequency and not magnitude. (88, 150) However, taken into account that both the weight and the blood sugar values increased, this could have been a contributing factor.

When examining the individual questions in the Smart Diet, the patients ate less low fibre bread, chose leaner meat as cold cuts, and more butter/margarine with highly unsaturated fat on bread/crisps from V1 to V2.

At the end of the study at V3, there was no longer a more frequent use of butter/margarine with highly unsaturated fat on bread/crisps. This is unfortunate since both the NCEP ATP III and the Norwegian Health directorate encourages using that instead of oils, butter and hard margarine with high amount of saturated fat. (35, 148) Furthermore, 2 grams (g) a day of plant sterols/stanols is recommended, as it can reduce LDL-C by 8-10%. (35, 148) The EAS consensus paper recommend that it should be considered in FH patients. (216) 25g of Vita Proactive gives 2g of plant sterols. This product was launched in Norway in 2006 and is included in the two latest Smart Diet versions, but not in the 2003 version used in this study. A double-blinded randomized cross over trial study (217) from Ullevål University hospital, showed that margarine added plant sterol reduced TC, LDL and ApoB significantly, when compared to a margarine with no added plant sterols, but had a similar amount of fat and fatty acid composition. Thus, margarine rich in unsaturated fat gave reduction in lipid values, but the added plant sterols gave a further reduction. Even though the magnitude of this question may not seem that important in this study, since one out of three of our patients did not use butter/margarine on bread at all, a constant focus on choosing correct types of fat is important. Especially, since the consumption of “real dairy butter”, in the general population increases every year. From 2008-2016 “real dairy butter” increased from 1.4 kg to 2.0 kg per person. (218) This “real dairy butter”- trend must not be accepted by the FH population.
A negative development was also observed in our patients concerning the choice of cheese. One out of three chose whole fat cheese products. This was a doubling compared to V1. If the consumption of cheese products has increased, as it have in the general population with 2.3 kg per person in the period from 2007-2016, the saturated fat intake is affected even more in the negative direction. (218) This is in strong contrast to the recommendations of choosing three portions of lean dairy products a day. (88, 148, 219) A special focus on eating lean dairy products is important since around 40% of the saturated fatty acids come from this food group. It is important to eat dairy products since over 60% of calcium and iodine comes from these products, but everyone are recommended to choose the leanest alternative. (148)

On the positive side our patients continued to choose bread with more fibre and lean meat as cold cuts. This is in line with the recommendations. (35, 88, 148) Eating more whole grains rather than white bread will increase dietary fibre intake. High intake of oats and barley, which contain the water-soluble viscous-forming fibre β-Glucan, can reduce TC and LDL-C by 5-10%. (154, 220) This, including the other health benefits associated with dietary fibre, gives the patient a better cardio-protective profile, and reduces the CV risk. (154, 221) In a pooled analysis cohort, every 10 g/d increment of dietary fibre was associated with 14% risk reduction in all coronary events, and a 27% decrease in coronary death. (155)

Concerning the reduction in red meat, cold cuts have less impact because of the smaller portion size compared to standard dinner portion size of meat. Eating both leaner products and less frequent, is a step in the right direction. 79.2% chose the leanest meat option for dinner in the Smart Diet at V3. It is the total amount of red meat that contributes to CVD, and it is not recommended to have an intake above 500g a week. (88) The Smart Diet does not ask about frequency of red meat intake, or the portion sizes. But if this is similar to the general Norwegian population, it is just slightly over recommended intake. This is a lower red meat consumption compared to other countries, such as Germany, France and Great Britain. (222)

Other cardio-protective changes the patients achieved during the observation time, were eating more frequent fish for dinner, and more vegetables a day. A fish-for-dinner consumption ≥ three a week was more than doubled at V3. Less than 20% ate fish once a week or less, implying that over 80% of the study subjects consumed the recommended fish intake for reducing CVD. (35, 88) Unfortunately, the Smart Diet did not differentiate between fatty fish or lean fish. Fatty fish is the main source of omega-3- fatty acid in the diet, and should be included as one of the three portions of fish a week. Fatty fish has no direct
hypocholesterolemic effect, but have shown to reduce CV risk as it has several CV benefits. (19, 147) Fatty or lean, fish has a low amount of saturated fat, and it is the highly preferred option instead of dinner choices with high saturated fat content. However, the most beneficial for CHD, is to replace the saturated fat with polyunsaturated fat. (146, 223) Choosing a fat fish for dinner instead of red meat will do just that.

The daily consumption of vegetables increased during the study. Eating two or more portions of vegetables a day increased with 10%, and over 70% ate two or more portions of vegetables a day at V3. 6% of the patients ate three or more portions of vegetables a day at V3. This is a fine improvement, however at V3 one out of three ate ≤1 portion of vegetables a day. Five portions of fruit, berries and vegetables a day is recommended, as they contain many vitamins, minerals, antioxidants and fibres. Half of the recommended intake should be vegetables. (88, 89) An intake up to 800g of fruit and vegetables combined a day, gives a CV risk reduction. (91) In the general Norwegian population a trend of increased vegetable intake is also seen, as the vegetable consumption have increased over 20% from 2005 to 2015. (224) If the avocado trend, that has hit Norway and the rest of the world, also include the FH patients, this is highly beneficial since avocado is rich in polyunsaturated fatty acids. (225)

Dietary supplementation consumption did not change much, with the exception of omega-3 capsules that decreased. It is difficult to assess this because dietary supplementation is based on the individual needs, and should therefore be assessed during consultation. Alcohol consumption did not change much during the study. Approximately 50% consumed 1-7 units a week, and 10% consumed more than this. The Smart Diet does not distinguish between type of alcohol. Some alcoholic drinks contain quite a lot of energy and can contribute to an increased weight, which have a negative effect on blood values. Others, like red wine contain polyphenols, which may have a potential positive effect on blood values. (73) Further increasing alcohol intake, is associated with increased levels of TG, which contributes to a more metabolic profile. (228)

The data relating to physical activity is the patients self-reported performances. Only half of the subjects followed the Nordic recommendations of at least three sessions a week. (88) This is disappointing low, especially since physical activity and reversal of sedentary behaviour both can prevent and reduce CV risk factors such as hypertension, insulin resistance and
glucose intolerance, elevated TG concentrations, low HDL-C concentrations and obesity. (93, 94)

One important positive development was a 30% decrease in number of smokers. Those who still remained smokers increased their smoking habits slightly, but not significantly. The smokers at V3 had been smokers for a median time of 34.5 years with a minimum of 7 year, and the longest one for 53 years. The majority of the smokers smoked heavily and reported ≥11 cigarettes a day. Even if 85% were not smokers at V3, close to half of them had been smokers earlier in life, with a median time of 14 years. This means that over half of the patients have increased their already high CV risk, since current smoking and cumulative exposure have been shown to be serious independent risk factors for CVD and CHD. (69) If their cohabitants were smokers they would also be exposed to second hand smoking and the cumulative exposure would be increased, but these data were not collected.

Patients preferences form
Interestingly there was significant difference in the answers from V1 to V3, in the statement “a low cholesterol is more important than not having adverse effects” from the patients preference form. More of the patients fully or partly agreed, that having low cholesterol was more important for them at V3 compared to ten years earlier at V1. The reason for this is unknown and could be multifactorial. It is scarcely described in the literature, but a few thoughts are deliberated. The number of people with CVD increased 10% during the study period, and over 60% of those who started the study with established CVD experienced a new CV event during the study period. The patient’s emphases of low lipid values may have increased because more patients experienced the horrible consequences that may occur with sustainable high cholesterol levels. Another aspect could be that they had lived for long periods with some adverse effects from LLM, which they could accept. A third point, and probably the most important, could be the continuous treatment effort done by the physicians over many years, to find and fin-tune medications and dosages minimize the adverse effects. Thus, with this medication the patient may have better compliance and it is easier to achieve low cholesterol levels.

As for the two other statements: “A healthy diet is as important as medicines” and “I prefer to have as low cholesterol as possible”, there were no significant differences in the answers, and the vast majority fully agreed. A point to mention is that even if the patients said that they believed a healthy diet and lifestyle is as important as medicines, their Smart Diet scores are
not so good. Less than 40% are in the highest category, furthermore under half have a physical activity level at recommended level and 15% are smokers at V3. (88)

5.2.2 Comparison between those with and without CVD at V3

Age and sex
Underdiagnosis and undertreatment of FH leads to missed opportunities to reduce early-onset CV morbidity and mortality. (15, 187) The FH patients with established CVD in this study had their first CV event at a highly premature age of 46 years. These patients measured their first high TC thirteen years prior to the first CV event, and single continued LLT started just five years prior to the first CV event. The late discovery of the disease in combination with late introduction of LLM, probably lead to a higher risk of development of CVD, since an optimal lowering of LDL-C over the lifespan reduces cumulative risk. (127) Compared to those without established CVD in our study, they were approximately 10 years older in every scenario; first measured high TC, first visit to the LC, and when they started single, double and triple medication. When the initial first step starts late, the others follow. The importance of cascade screening and early diagnosis seems more and more important for the treatment of these patients.

Patients with CVD at V3 were significantly older, a reflection of the progressive accumulation of coronary atherosclerosis and the cumulative exposure to atherogenic risk factors, and the late start of LLT. (35) There were predominantly men among those with CVD, but the sex distribution was not significantly different for those with and without CVD. Even though the male sex are predicted to have a higher accelerated CV risk in the general risk assessments, the women in this study were later aware of their high cholesterol and started LLM significantly later, this may have led to an earlier age of development of CVD for the women. (31, 186)

Lipid values and LLM
The untreated levels of TC and LDL were significantly higher for those with CVD. Partly, the reason for this could be because those with CVD had measured TC and LDL at a higher age, and subsequently started LLM late in life. We cannot exclude that the patients with CVD, originally had higher lipid values than those without.

There were small differences to detect in the blood lipid values at V3, probably because the CVD group was treated more intensively. More patients with CVD were on high intensive statin treatment and used more types of LLM. Again, this may be a reflection of both higher
untreated lipid values and a later diagnosis and treatment start. However also the other facts, including MetS, diet and lifestyle will aggravate these lipid values. These factors should be more in focus, especially when these data show that an intensive LLM treatment cannot do all the work. Because even with this intensive treatment, much needed to compensate for the excess risk of established CVD, the patients were far from ideal LDL-C levels, with over 50% higher levels than LDL-C treatment target for secondary prevention. (30, 35, 173) Half of those who did achieve LDL-C treatment goals in secondary prevention used PCSK9-inhibitors, which imply that ordinary treatment with statin, Ezetimibe and colesevelam is not enough.

**Metabolic profile**
The metabolic blood values were all significantly higher for those with CVD, with the exception of HDL-C. The median fasting glucose and HbA1c levels were close to reaching pre-diabetic levels, using the cut off values for American diabetes association. (212) Furthermore 73% of those with CVD had antihypertensive treatment, fulfilling yet another criteria in the MetS definition. The average WC was high in both sexes, and significantly higher for men with CVD compared to those without. The overall more metabolic risk factors present in those with CVD, resulted in twice as many diagnosed with MetS. This is highly concerning since this increases the already high risk of FH patients with establish CVD of new CV events and mortality. (77, 79, 187)

There was significantly higher occurrence of MetS among the men with CVD, than those without CVD. This was significant both for those over and under 55 years of age. The men with CVD had significantly larger WC, and a strong tendency toward a higher BMI compared to those without. If they had the same body similarities before they got CVD this may have been a contributing factor, as accumulation of visceral fat increases the CV risk. Having MetS on top of the established CVD, their risk is even more increased for developing a new CV event. (77) However as discussed before, WC do not have the ability to differentiate between visceral and subcutaneous fat, and the conclusions could have been stronger with the addition of hip circumference.

**Diet and lifestyle**
Experiencing a CV event is scary and the thoughts of death may be close by. Many people would therefore try to live healthy in effort to reduce the probability of a new CV event. So, it is not surprising, that those with CVD scores significantly higher in the Smart Diet questionnaire. The patients with CVD eat less whole fat cheese, and more frequent fish on
bread/crisps and fish for dinner at V3. The rest of the Smart Diet questions were not significantly different from the patients without CVD. However, as discussed previously the whole study group had a more cardio-protective diet and eat more portions of vegetables a day, chose leaner meat as cold cuts, and ate less frequent low fibre bread at V3. Still the main improvements on the diet at V3, were reaching recommend levels of fruit and vegetables consumption, choosing low fat dairy products, and eating less candy/chocolate/biscuits etc.

As previously discussed, the main focus of the Smart Diet is on saturated fat intake. Fish is fish, portion sizes, processed or not, lean or fat, is not distinguished. The same is for almost all of the Smart Diet questions. Especially, since the CVD group have a BMI closer to be defined as obesity than normal, they are on the range to prediabetic levels of fasting glucose and HbA1c, and almost three out of four have antihypertensive treatment a greater focus on portion sizes, sugar and salt intake should take place.

The dietary pattern may have had effect on the of development of the CVD for the patients in this study, however consistent data on dietary patterns before the CV event happen, is not gathered since most of the patients had CVD before enrolment.

The level of physical activity was the same for those with and without CVD, and under 50% achieved the Nordic recommendation. (88) The heart is a muscle that needs exercise. Daily physical activity is strongly recommended rather than a sedentary lifestyle, and the benefits of lower pulse, lower BP, weight balance, better lipid and metabolic blood values, contributes to reduce the risk of a CV event, both new, recurrent and also CV mortality. (93, 94, 226) This makes physical activity essential for all people. Physical activity in patients with CVD, is likely to reflect longstanding patterns of exercise as well as change in physical activity since the diagnosis. A person who has done a lot of physical activity all his/her life will in most cases continue with this, but some will be cautious of vigorous exercises in fear of a new CV event. A large international study (227) concluded that the majority of the sedentary CHD patients were not limited “a lot” by cardiac symptoms, suggesting that they could actually have been more active than they are.

Alcohol consumption was the same in both groups. Approximately 50% drank 1-7 units a week. This is a moderate alcohol consumption which compared to non-drinkers and heavy drinkers may exhibit a cardio-protective benefit. (32, 72, 73) However the data was collected
after they had experienced a CV event, so we cannot know if their drinking habits have actually had a protective or harmful effect, or if they changed drinking habits after the CV event.

Approximately 15% smoked in both groups, and there was a tendency to slightly more former smokers in the CVD group. This may suggest that smoking habits could have contributed to increased CV risk. This was seen in the INTERHEART study, were both current and former smokers had an increased risk of MI up to 3.0 fold higher, than non-smokers. Increased smoking intensity and length, increased the MI risk. (32) Quitting smoking, or at least reducing the number of cigarettes, is usually a subject at each consultation, since smoking is the most preventable cause of premature death. (65, 70)

Cardiovascular death
The first CV event occurred when they were in average 46.6 years old. This is close to the same premature CV age as seen in the CASCADE FH registry study and the SAFEHEART study. (176, 183) A second CV event occurred in over 70% of those with CVD. In a recent study from Norway the average age at time of death for FH patients were approximately 60 years, the same was reported in this present study. (17, 187) In comparison, life expectancy in the general population in Norway in 2016 was 80.6 years and 84.2 years for men and women, respectively. (229) This underlines that CV morbidity and mortality is high in FH patients. (187) Furthermore, most FH patients are reported to have established CVD at time of death, and in 50% of the cases CVD is the cause of death. (17) Half of the patient who died during this study was also reported to have CVD at time of death, or that CVD was the cause of death. Four out of the six with CVD had been heavy smokers for decades. This has very likely contributed to their CVD, as previous studies have shown. (32, 69)
6 Conclusion

1. In this study the patients were diagnosed late and this contributed to a late start of LLM.
   - TC was first measured in average at 26.8 years old.
   - LLM was started in average at 31.9 years and 37.8 years in men and women, respectively.
   - Only 22% of the women started LLM before having children.
   - Those with CVD were in average 33.7 years when they measured their first and 41.2 years when they started with LLM, that was 9.8 years 9.7 years, respectively, older than those without CVD at V3. Those with CVD had also significantly higher untreated TC and LDL-C.

2. LLM was intensive and used by most of the patients, and some suffered from adverse effects.
   - Over 90% used statin treatment, the majority used high intensive statins, and close to half in combination with Ezetimibe at V3. No differences in statin intensity were seen when comparing those with and without CVD at V3.
   - 30% used three or more LLM medication, significantly more of those with CVD.
   - 8% used PCSK9-inhibitors, no differences were seen when comparing those with and without CVD at V3.
   - 16 patients did not use statin therapy, 13 of these was not because of pregnancy, and for them the main reason for discontinuation of statin treatment was adverse effects of LLM. The average length of statins was 4.0 years. They were mostly women with highly elevated blood lipids and three suffered from CVD.
   - For those on LLM treatment, one out of three had adverse effects of statin and colesevelam treatment, mainly muscular and gastrointestinal complaints, respectively.

3. >50% reduction of untreated TC and LDL levels was achieved, however few reached LDL-treatment targets set by EAS.
   - 30% reached the target in primary prevention, 49% when including those close to target.
   - 8.5% in secondary prevention, where 50% used PSCK9-inhibitors, when including those close to target it raised to 25.5%, where 17% used PCSK9-inhibitors.
   - TC, LDL-C, TG, ApoA1, ApoB all increased during the study. However, they were not significantly increased for those with CVD compared to those without.
4. The increased in weight, and metabolic risk factors became more severe during the study
   - One out of three men had abdominal obesity at V3. A higher prevalence for those with than without CVD was seen.
   - Three out of five women had abdominal obesity, and there was no difference among those with or without CVD.
   - HbA1c and fasting blood glucose increased over 8-10 years, and reached the range of pre-diabetic levels. Those with CVD had significantly higher values. 10% used glucose lowering medication, no differences with or without CVD.
   - Average BP did not increase, and was not at hypertension levels. However, >70% of those with CVD at V3 used antihypertensive medication.
   - One out of four men had MetS. Over half of the men with CVD had metabolic syndrome, this was significantly higher compared to those without CVD.
   - One out of three women had MetS, no significant difference between those with and without CVD was seen.

5. The diet became more cardio protective over the observed years.
   - 39% scored in the highest Smart Diet category, and only 3% in the lowest at V3.
   - As a group, they increased the frequency of fish for dinner, and portions of vegetables a day, they choose more lean meat as cold cuts and less frequent low fibre bread. Whole fat cheese consumption however, increased.
   - On the down side >40% reported a consumption of candy/chocolate/biscuits etc. 2-3 times a week, 34% eat whole fat cheese, 34% eat ≤1portion of fruit/berries/juice a day, 30% ≤1portion of vegetable a day, 21% eat fish for dinner ≤ once a week.
   - Those with CVD achieved a higher Smart Diet score, mainly due to a higher fish consumption and lower amount of whole fat cheese.

6. The physicians should have a greater focus on lifestyle changes. Even though the number of smokers decreased by 30%, the remaining smokers did not reduce the frequency of cigarettes per day. As regards to physical activity levels, these were low throughout the study.

7. The patients believed in a healthy diet and they wanted a low cholesterol.

8. Age at first CV event was highly premature, and so was the age for the 12 dead.
7 Clinical implications and future perspectives

Our findings suggest that the FH patient in this population were diagnosed late, and subsequently starts LLM late. The women in our study started even later than the men with LLM. With early detection and treatment the women would have the opportunity to be well treated, and incorporate healthy dietary and lifestyle habits before their childbearing years. This is important, because in the conceiving, pregnancy and lactation periods, statins and Ezetimibe are discouraged. Cascade screening of the relatives of FH patients should be emphasised, together with increased knowledge among the general practitioners, and the public. This process has already started.

Further, our findings suggest that patients with FH have considerable difficulties with reaching treatment targets in primary and especially secondary prevention. This is despite intensive LLT, which might implicate a need for more efficient therapies. The new era with PCSK9-inhibitors have started the last years, but still relatively few patients in our sample used this medicine.

Despite frequent contact with health care professionals, FH-patients in our study tended to develop toward MetS. To avoid the development of MetS, it is important that health professionals’ measures anthropometric data and initiates actions, if unfavourable trends are seen. Dietary counselling, an established and important part of the treatment provided at the LC, should be more available for the FH patients. There should be more focus on portion size, salt and sugar intake, these are aspects the Smart Diet do not cover that well. Furthermore, the importance of fruit and vegetable intake, and last but not least, the substitution of saturated fat with unsaturated fat in every food group should be a focus in every consultation. A clinical nutritionist will have more knowledge and advice to the patients regarding this. Further, the importance of physical activity should also be emphasized more, together with motivation to stop, or at least reduce, smoking.

Perspectives should be to complete V3 for all the patients who attended V1. A special emphasis should be to reach the subjects who no longer are patients at the Lipid Clinic. Then a comparison could be made between those who are treated at an established lipid clinic, and those who are not. Comparison between this FH population and a non-FH population regards to dietary and lifestyle habits could also be quite interesting. Proceeding with new visits in the future is of interest to follow their future risk of MetS, CVD and premature death, especially if it could be more widespread use of the promising PCSK9-inhibitors.
8 Conflicts of interest
The supervisors have in the past received honoraria for lectures and board fees. 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, Genzyma, Drammen Revmatiker forening and the Norwegian Heart and Lung Patient Organization.

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


156. Mork I. 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 patient with Familial Hypercholesterolemia [Master]: University of Oslo 2016
157. Thorvall M. Treat To Target Familial Hypercholesterolemia – A prospective study on effects from maximal high intensive treatment of FH patients during eight years [Master ]: University of Oslo 2015.
165. Thorvall MS. Treat To Target Familial Hypercholesterolemia -A prospective study on effects from maximal high intensive treatment of FH patients during eight years. 2015.
178. Lov om humanmedisinsk bruk av bioteknologiloven m.m (bioteknologiloven) 100. Sect. 5-9 (2003).
20. Sang S, Chu Y. Whole grain oats, more than just a fiber: Role of unique phytochemicals. Molecular nutrition & food research. 2017;61(7).


Appendices

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

Appendix 2  Study invitation with written informed consent

Appendix 3  The patient’s preference form


Appendix 5  The Clinical Report Form

Appendix 6  Approval by the Regional Committee for Medical and Health Research Ethics
### Appendix 1 The Dutch Lipid Clinic Network diagnostic criteria of Familial hypercholesterolemia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Point</th>
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<tbody>
<tr>
<td><strong>Family History</strong></td>
<td></td>
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<tr>
<td>First-degree relative with known premature* coronary and vascular disease OR First-degree relative with known LDL-C level above the 95th percentile.</td>
<td>1</td>
</tr>
<tr>
<td>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.</td>
<td>2</td>
</tr>
<tr>
<td><strong>Clinical History</strong></td>
<td></td>
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<tr>
<td>Patient with premature* coronary artery disease.</td>
<td>2</td>
</tr>
<tr>
<td>Patient with premature* cerebral or peripheral vascular disease.</td>
<td>1</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
<td></td>
</tr>
<tr>
<td>Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis prior to age 45 years.</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cholesterol levels mg/dL (mmol/liter)</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C &gt;= 330 mg/dL (≥ 8.5)</td>
<td>8</td>
</tr>
<tr>
<td>LDL-C 250 – 329 mg/dL (6.5 – 8.4)</td>
<td>5</td>
</tr>
<tr>
<td>LDL-C 190 – 249 mg/dL (5.0 – 6.4)</td>
<td>3</td>
</tr>
<tr>
<td>LDL-C 155 – 189 mg/dL (4.0 – 4.9)</td>
<td>1</td>
</tr>
<tr>
<td><strong>DNA Analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Functional mutation in the LDLR, apo B or PCSK9 gene</td>
<td>8</td>
</tr>
<tr>
<td><strong>Diagnosis (diagnosis is based on the total number of points obtained)</strong></td>
<td></td>
</tr>
<tr>
<td>Definite familial hypercholesterolemia</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Probable familial hypercholesterolemia</td>
<td>6 – 8</td>
</tr>
<tr>
<td>Possible familial hypercholesterolemia</td>
<td>3 – 5</td>
</tr>
<tr>
<td>Unlikely familial hypercholesterolemia</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>

*Premature = < 55 years in men; < 60 years in women
Ny konsultasjon ved Lipidklinikken og ved TTT-FH – prosjektet

Kjære pasient


Det innebærer at du fyller ut det SmartDiet-skjema som vi brukte på den tiden. Vi ønsker å få vite hvordan du har det, og hva du mener om oppfølgingen ved at du fyller ut et spørreskjema som tar opp spørsmål knyttet til det.

I tillegg vil vi kartlegge alt ved å intervju deg grundigere enn vanlig, og vi fyller ut spørreskjemaer vedrørende endringer i medisineringen, bivirkninger og plager, hjertekar- og andre sykdommer, og livsstilsforhold og jobbsituasjon. Det foretas også et eget intervju med vår masterstudent i klinisk ernæring, hvor dere gjennomgår kosten og livsstilen grundig.

Siden dette ingår i et vitenskapelig prosjekt, skal du ikke betale egenandel. Du vil få dekket reisegift på vanlig måte.

Arbeidet vil bidra til å avdekke svakheter ved vårt arbeid, og hjelpe oss til å forbedre dette. - Vi håper at du vil kunne være med!

Dato 20.12.16

Med vennlig hilsen

Kjell-Erik Arnesen
overlege

Karoline Randsborg
klinisk ernæringsfysiolog masterstudent
Telefonintervju ved Lipidklinikken vedrørende TTT-FH – prosjektet

Kjære pasient!

Vi vil få invitere deg til et telefonintervju ved Lipidklinikken. I samtale med vår masterstudent i klinisk ernæring, Karoline Randsborg, vil kosten og livsstilen kartlegges.


Under intervjuet fyller vi ut det SmartDiet-skjemaet, som vi brukte på den tiden. Vi ønsker videre å få vite hvordan du har det, og hva du mener om oppfølgingen ved Lipidklinikken og vi fyller ut et spørreskjema som tar opp spørsmål knyttet til det.

Siden du var til konsultasjon i 2016 ber vi om å få bruke journalnotater for opplysninger vedrørende endringer i medisinering, bivirkninger og plager, hjertekar- og andre sykdommer, samt livsstilsforhold.

Prosjektet vil bidra til å avdekke svakhetene ved vårt arbeid, og hjelpe oss til å forbedre dette. - Vi håper at du vil kunne være med!

Vennligst kontakt Lipidklinikken, ved Karoline Randsborg, for avtale tid og dato for intervju. Hører vi ikke fra deg, tillater vi oss å ringe deg om dette.

Dato 22.05.17

Med vennlig hilsen

Kjell-Erik Arnesen
overlege

Karoline Randsborg
klinisk ernæringsfysiolog masterstudent
Tlf: 91008704 (hverdager 09-15.00)
Forespørsel om deltakelse i forskningsprosjektet

"Treat To Target Familiær Hyperkolsterolemii"

Bakgrunn og hensikt
Ved dette spør vi deg om å delta i oppfølgningen av forsknings- og kvalitetssikringsstudien som du deltok i årene 2006-07, Treat To Target – FH studien. Man foretar nå en 8-9 års oppfølgning, 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

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

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

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 der 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)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

(Navn med blokkbokstaver)
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)

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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!**
20 spørsmål om ditt kosthold og din livsstil

Copyright: Ulliklinikken AS, Rikshospitalet

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

Les spørsmålene og de angitte svarmulighetene nøye!
Angi gjørne 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
- Kulturremelk
- Kefir
- Kaffemelk 5% fett
- Lettmelk
- Cultura
- Biola
- Ekstra Leit melk
- Skummet melk
- Skummet kultur melk
- Biola bærer melk (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
- Plått fløte
- Crème Fraîche
- Setrørømme
- Kaffefløte
- Matfløte
- Vikingmelk
- Kesem (8% fett)
- Rømmeölle
- Lettrømme
- Bruker fløte eller rømme én gang eller sjelden i uken

3. Brød, knekkebrød og andre komprodukter
Hvor mange skiver brød / knekkebrød eller porsjoner kornblanding spiser du daglig? Antall:_____

Hvor mange måltider med fine komprodukter spiser du?

"Vanlig" kneipp • finbrød • fritt hjemmefakt og kjøpe brød • loft • fine rundtykker • lyst knekkebrød • baguetter • riskaker • puffet ris • cornflakes • høvrenatter • 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 komprodukter
4. Smer, margarin på brødmaten
Hvilken type bruker du oftest?
Melange margarin • Per margarin • Soft fløra stekemargarin (kube) • Soya stekemargarin (kube) • Soft margarin uten salt og melk • Løtta
Soft Flora (beger) • Soft Light • Soya margarin (beger) • Soya lett margarin • Oliven margarin • Olivers • Solvik margarin
Vita • Vita lett • Omega
Bruker vanligvis ikke smer 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) • Nækkost (F42) • Gudbrandsdalsost (G39) • Elke getost • Inntilmysost • Edamer • Gråost • "Dessert ost" • Smørrett fatost (H50 og fetete) • Mozzarella (mer enn 20% fet) • Fete ost (mer enn 20% fet) • Revet pizza/pastaost • Taffelost • Burgerost • Snedrik, smørrett getost • Parmesan
Lettere hvitost • Lettere nækkost • Letteres flettemysost • Letters Gudbrandsdalsost • Smørrett ost (18% fet) • Mozzarella (16% fet) • Fetaost (20% fet) • Prim med vaniljesmak
Cottage cheese • Germalost • Pultost • Mager myost • Prim • Mager prim • Smørrett magerost
Bruker ost to ganger eller sjøldnere i uken, eller bruker aldri ost

6. Kjøtt pålegg
Hvilken type bruker du oftest?
Leverpostei • Salami • Lett salami/spiselsalami • Service • Fårepølse • Falukorv
Fleseskølp • Mørpkølp • Reinseppel • Stabburpellier • Sylte • Lømmerull
Lett/mager leverpostei • Løt service • Delikat ovnsbakt postei
Børnekløtt • Kalkun pålegg • Kylling pålegg • 3% servelat (Det Sunne Kjøkken) • 3% leverpostei (Det Sunne Kjøkken) • Kolverull • Okservull • Skikke kold/røkt • Hamburgenygg • Annet kjøtt uten synlig fet
Bruker ikke kjøtt pålegg ukentlig eller bruker aldri kjøtt pålegg

7. Fisk pålegg
Hvor ofte har du fisk pålegg på brødmaten?
Laks • makrell • sild • sardiner • brisling • tunfisk • reker • krabbe • crab-sticks • fiskepudding • fiskekaker • Havbrøl etc.
På inntil 1 brødske i uken, eller aldri
På 2 til 4 brødskiver i uken
På 5 eller flere brødskiver i uken

Side 2
8. Majones, majonespålegg

Hvor ofte har du majonespålegg på brødmaten?

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

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

På 2 til 7 brødskiver i uken ..........................................................................................................................................

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

9. Kjøtt til middag

Hvilken type bruker du oftest?

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

Grillpølse • Wienerpølse • Kjøttkaker • Knakkpølse • Takkeltøttet med fettrand • Lammekoteletter • Medisterfarse • Medisterpølse • Medisterdill • Medisterkake • Wienserschnitzel • Fylsår • Bacon med fettrand • Flekk • Grillben • Fårekjøtt • Pinnekjøtt • Ribbe • And • Æde ........................................................................................................................................

Kjøtt- • Kjøttkaker • Kjøttkaker • Kjøttkaker • Hamburger • Kababkjøtt • Leitpølse • Kyllingpølse • Kamkoteletter med fettrand • Nakkekoteletter uten fettrand • Kylling med skin • Hene med skin • Kalkun med skin • Blodpølse • Bayonneskinke med fettrand • Hamburgerrygg med fettrand ........................................................................................................................................

Kjøtt uten synlig fett • Karbonadefett • Biff • Stek uten fettrand • Eggkinke • Kamkoteletter uten fettrand • Petersel • Eplekorv • Kjøttkaker og Karbonader med 3% fett ("Det Sunne Kjøkken") • Grill- og kjøttterre med 9% fett ("Go' og Mager" fra Gløde) • Viltkjøtt • Kalv • Lamm indreilet • Hane uten skin • Kylling uten skin • Kalkun uten skin ........................................................................................................................................

Spiser ikke kjøtt ukentlig, eller aldri ........................................................................................................................................

10. Fisk til middag

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

Inntil en gang i uken eller aldri ......................................................................................................................................

2 ganger i uken ..................................................................................................................................................................

3 eller flere ganger i uken ..............................................................................................................................................

11. Fett i matlagingen

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

Mellomser • Tine smer (mykere) • Tine seremær • Bremyrk • Smøreod • Melanger margarin (kube) • Per margarin (kUBE) • Soft Flora stekemargarin (kUBE) • Soya stekemargarin (kUBE) ........................................................................................................................................

Soft Flora (bøger) • Soya margarin (bøger) • Solsikke margarin • Oliven margarin • Oliveno ........................................................................................................................................

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

Bruker vanligvis ikke fett i matlagingen ........................................................................................................................................

Side 3
12. Grønnsaker
Hvor mange porsjoner grønnsaker, kokte og/eller rå, inkludert poteter, spiser du daglig?
1 porsjon = 150 g; 2 dl grønnsakblanding, 3 dl blandet salat, 2 guirreeter, 2 poteter o.l.
0 til 1 daglig .................................................................
2 daglig ........................................................................
3 eller flere .................................................................

13. Frukt, bær, juice
Hvor mange porsjoner spiser/drikker du daglig?
1 porsjon = 150 g; 1 appelsin, 1 eple, 20 dver, 2 dl bær, 1,5 dl juice o.l.
0 til 1 daglig .................................................................
2 daglig ........................................................................
3 eller flere daglig ........................................................

14. Sukker, sett pålegg og sett drikke
Hvor ofte spiser/drikker du dette?
1 brødkive med honning, syltetøy, prim, brunost, sjokoladesnack eller annet sett pålegg; 1 glass sukker
sett, brus, juice eller nectar; 5 sukkerbiter; 1 skje sukker

0 til 2 ganger daglig ......................................................
3 til 4 ganger daglig ......................................................
5 eller flere ganger daglig .............................................

15. Godteri, sjokolade, snacks, kaker, fet kjeks, iskrem
Hvor ofte spiser du dette?
Bortsett fra: Nødder • mandler • marsspan • hjemmemasset popcorn • sukkerfrie godterier •
vingummi • drops • pastiller • mager bakst (som sjøbakst) • saftis, yoghurtis, sorbet

1 gang i uken eller sjekkere ...........................................
2 til 3 ganger i uken .....................................................
4 eller flere ganger i uken ...........................................

Antall poeng: ................................................................
5 spørsmål om din livsstil

Kjønn  ○ Mann  ○ Kvinne  
Høyde ___ cm  
Alder ___ år  
Vekt ___ kg

1. Vekt
Jeg ønsker å gå ned i vekt  ○ Nei  ○ Ja

2. Røyker du?  ○ Nei  ○ Ja  ○ Ja, selskapsrøyker

Hvis ja, hvor mange sigaretter/piper røyker du per dag?
○ Mindre enn 1  
○ 1 til 5  
○ 6 til 10  
○ 11 til 20  
○ Mer enn 20

3. Drikker du alkohol?  ○ Nei  ○ Ja

Hvis ja, hvor mange enheter alkohol drikker du til sammen per uke?
1 enhet =  
1 glass vin (125 ml)  ○ Mindre enn 1  
1 glass øl (0.33 l)  ○ 1 til 7  
4 cl brennevin (drink, konjak, likør)  ○ 8 til 14  
○ Mer enn 15

4. Hvor ofte mosjonerer du i minst 30 minutter?
Rask gange, løping, skigåing, svømming, sykling etc.
○ Aldri  
○ Sjeldnere enn 1 gang per uke  
○ 1 til 2 ganger per uke  
○ 3 eller flere ganger per uke

5. Bruker du kosttilskudd?
○ Nei  
○ Tran  
○ Fiskeoljekapsler/omega3-kapsler  
○ Multivitamin  
○ Annet: __________________________
Kostholdsvurdering

29 poeng eller mindre: Du bør forbedre kostholdet ditt på mange punkter for å gjøre det mer helse- og hjertevennlig

30 til 37 poeng: Du kan forbedre kostholdet ditt på en del punkter slik at det blir mer helse- og hjertevennlig

38 poeng eller mer: Du har sunne kostholdsvaner

Kommentarer:

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

Skjemaet er vitenskapelig bedømt i forhold til ved kostholdsregistrering, med unntak av spørsmål 14 om sukker. Evalueringen ble publisert i tidsskriftet "Nutrition, Metabolism and Cardiovascular Diseases" i 2002.
De gode rådene finner du her

Mettet fett er kolesteroløkende. Reduser derfor innmat av matvarer med mettet fett. Velg i stedet matvarer med mye umettet fett som kan senke kolesterol.

- Drik mager melk, 1/2 liter skummet, søt eller sur, daglig. Dersom du ikke dricker melk daglig, kan det føre til en reduksjon av kalsium.
- Alle fleke- og rømmetyper inneholder mettet fett, og mettet fett øker kolesterolholdet. Myk plantemargarin er en god kilde til umettet fett. Velg typer med mer enn 70 % umettet fett.
- Frisk skink og kyllingskinner inneholder mye mettet fett og bør unngås.

Antall poeng: ____________________

25 spørsmål om ditt kosthold og din livsstil
Copyright: Lipidklinikken®, Medinnova, Rikshospitalet. Kopiering av dette skjemaet er ikke tillatt.

Les spørsmålene og de angitte svarmulighetene nøye! Sett kryss ved det svaret som passer best med det du vanligvis spiser.

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 helbredeligt.
31 poeng eller mer: Du har sunne kostholdsvaner.

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


Kommentarer:
### 1. Måltidsmønster

Hvor mange måltider spiser du daglig?  
- 1 til 2 måltider  
- 3 måltider  
- ...

- 5 eller flere brødskiver per uke

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<th>11+</th>
<th>Totalt antall:</th>
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### 2. Fløte, ramme og lignende.

Ifølge brukeren/mL bruker du ofte middagstidene, i dress, i spis eller i kaker, i kaffelatte og så videre.

- Kremkaffe • Cremelatte • Sætemelk • Flødekrem
- Lattemelk • Leatte melk • Kaffelatte • Bottele lattemelk • Vinklemelk • Kesam Mjølghurt.

Bruker ikke ukert eller bruker aldri.

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

Hvor mange porsjoner ost bruker du daglig?  
- (eks. pizza, fettet mat, hamburgere, lasagne,)

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### 4. Kjøtt og pølse

Hvilken typer kjøtt og pølse bruker du ofte?

- Løvepostei • Salami • Lett salami • Servelat • Fårepølse • Stabburpølse • Wienerschnitzel • Bacon • Flesk • Grillben • Fårekjøtt

### 5. Kjøtt til middag

Hvor ofte har du kjøtt på middagen?

- Familiedeler • Med sterker • Grillpostei • Vænerspostei • Kjøttfløte • Med sterkpostei • Kjøttfløte • Med sterkpostei • Kjøttfløte • Med sterkpostei • Kjøttfløte

### 6. Fiskepølse

Hvor ofte har du fiskepølse på middagen?

- Eksempler: Laks • Matløv • Sjokoladekaker • Bush • Reiselærke • Reiselærke • Sjokoladekaker • Bush • Reiselærke • Reiselærke

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### 10. Brus og alkohol

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

- Eksempler: Laks • Maita • Krydderskinke • Pastramiskinke • Roastbiff • Bankekjøtt • Kylling- og kalkunpølse • Lett servelat • Kalverull • Spekeskinke uten synlig fett • Kylling, kalkun og høne uten skinn • Skiveskinke med fett

### 11. Fett i matlagingen

Hvor mye bruker du ofte til steking, baking, i saus, som dressing og så videre?

- Lyt kvalitet Fett • Kylling og kalkunfett • 4 porsjoner eller mindre

### 12. Brød, knekkebrød og andre kornprodukter

Hvor grove kornvarer bruker du?

- Eksempel: Roter pizza-/pastaost • Taffelost • Burgerost • Snøfrisk • Parmesan

### 13. Grønsaker, frukt og bær

Hvor mange grønsaker griner du?

- Eksempel: Våtskott • Sjokoladekaker • Bush • Reiselærke

### 14. Bærløse

Spiser du bærløse ukentlig?

- Eksempel: Hvit tomatbønner, brune bønner, kikkerer, friske fjerder, sukkererter.

### 15. Polet, ris og pasta

Hvor mange porsjoner polet, ris og pasta spiser du daglig?

- Eksempel: Spisere tinder 2 pølser og 1 drikke eller 1 drikke og 1 orkost ud af pølser og spatet.

### 16. Sukker, søtt pålegg, søtt drikke, kaker, kjeks og annen snacks

- Sjokoladekaker som potetgull, ostekakter, bonnehver, tortillas chips og så videre.

### 17. Nøtter og mandler

- Sjokoladekaker eller annet sukkerbuk ukentlig.

### 20. Egg

Hvor mye egg inkludert i matlaging, spise eller drikke?

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### 21. Alkohol

Bruker du alkohol?

- Eksempel: Hvis ja, hvor mange enheter drikker du i sammenslutning?

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<tr>
<th>Mindre enn 1</th>
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<th>11-15</th>
<th>Mer enn 15</th>
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### 22. Pynter

- Eksempel: Hvis ja, hvor mange kilo ønsker du å gå ned i vekt?

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### 24. Snuser

- Eksempel: Hvis ja, hvor mange porsjoner snus per dag?

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### 25. Fisk

Hvor ofte har du fiskepålegg på brødmaten?

- Eksempel: Laks • Maita • Krydderskinke • Pastramiskinke • Roastbiff • Bankekjøtt • Kylling- og kalkunpølse • Lett servelat • Kalverull • Spekeskinke uten synlig fett • Kylling, kalkun og høne uten skinn • Skiveskinke med fett

### 26. Baslerke

Hvor mange ganger per uke bruker du ost?

- Eksempel: Hvis ja, hvor mange porsjoner ost bruker du daglig?

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### 27. Selvbetjening

Hvor ofte har du fiskepølse på brødmaten?

- Eksempel: Hvis ja, hvor mange porsjoner fiskepølse du daglig?

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### 28. Kaffe

Hvilken type kaffe?

- Eksempel: Føls, cappuccino, kaffé, kaffé, frøkostkaff, prøvemelke.
De gode rådene finner du her

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

Drik mager melk, 1/2 liter skummer, søt eller sur, daglig. Dersom du ikke dricker melk daglig, kan det føre til et for lavt inntak av kalium.

Alle flede- og rømme typer inneholder mye mettet fett og anbefales ikke i hverdags kostholdet. Cultura, skummet kultur, lemmelk, ekstra lemmelk, skummet melk, yoghurt og Kestam (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 bredskiver. Vær også oppmerksom på mengde og type ost du bruker i matlagingen.


Spis alle typer fisk til middag flere ganger i uken. Fet fisk som makrell, sild, lax og ørret inneholder umettet fett (omega-3) og er derfor spesielt gunstig i hverdags kostholdet. Grove kornprodukter er viktig i hverdags kosthold. Økende mengde av mettet fett. Velg kornprodukter fremfor tyveløs, råkorn og lignende.

Spis alle typer fisk fritt som pålegg. Spis mye av alle sorter fiberrike kornprodukter. Havre er spesielt gunstig og bør brukes regelmessig. Brodet bør inneholde mer enn 15 gram fiber pr 100 g brød. Se også etter brødskalens på emballasjen.


Nøtter og mandler inneholder gunstig umettet fett, og mengde kaffen som bør brukes. Husk at kaffe tilsatt melk (for eksempel Cafe latte, cappucino) kan være en kilde til mettet fett avhengig av melketypen som brukes og mengde kaffen som benyttes.

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

1. Måltidsmønster
   Hvor mange måltider spiser du daglig? 1 til 2 måltider 3 måltider ... 5 eller flere brødskiver per uke.

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

3. Øst på bordmåten, i matlagingen, på pizza o.l.
   Hvor mye øst som pålæge, regnet i serveringer eller i skipsreiskaker.
   
4. Kjøttplekk
   Hunne type kjøttplekk bruker du? først,
   Mejeriprodukter, bl ant tre som høyeste karbonstoffer.
   
5. Kjøtt middag
   Hvor mange serveringer kan du fieste? 1 porsjon=150g som tilsvarer ca 2 gulrøtter eller ca 1 1/2 eple.

6. Fiskplekk
   Hvis du kan bli allerede.
   
7. Fisk til middag
   Hvor mange ganger i uken spiser du fisk, fisksmat og/eller fisleretter?
   Minst engang i uken eller aldri.
   
8. Mønster, remulade og kaker
   Hvor ofte bruker du mønster, remulade og/eller kaker på bordmåten?
   Eksempel: Mønster, remulade, fiskekaker.

9. Smør eller margarin på bordmåten
   Hvilken type bruker du? først,
   Olje • Flytende margarin • Vitas.

10. Brød, knekkebrød og andre kornprodukter
    Hvor mange skiver, rundstykker eller knekkebrød spiser du daglig? Antall:...........

11. Fett i matlagingen
    Hvor mye fett bruker du i matlagingen?
    
12. Bred, knekkebrød og andre kornprodukter
    Hvor mange skiver, rundstykker eller knekkebrød spiser du daglig? Antall:

13. Grønnsaker, frukt og bær
    Hvor mange porsjoner grønnsaker, frukt og bær spiser du daglig? Antall:

14. Bæltetjek
    Spiser du bildegrader, buie, bæltetjek, eller andre slike?
    
15. Polet, ris og pasta
    Hvor mange porsjoner polet, ris og/eller pasta spiser du daglig?
    
16. Sukker, sot, pålegg, sot, drikke, kaker, kjeks og annet snacks
    
17. Nøttet og mandiler
    Spiser du røtt eller mandiler?
    
18. Kaffe
    Drikker du kaffe?
    
19. Alcohol
    Drikker du alkohol?
    
20. Ei
    Hvor mange egg inkludert i matlagingen, spise du per uke?

---

**Totalt antall poeng:**
Appendix 5 The Clinical Report Form

<table>
<thead>
<tr>
<th>Medikament/Helsekost etc (navn)</th>
<th>Grunn, indikasjon</th>
<th>Startet dato dag/md/år</th>
<th>Sluttet dato dag/md/år</th>
<th>Brukes fortsatt JA</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dagens medikament</th>
<th>Tidligere medikament</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bivirkning 1-3

<table>
<thead>
<tr>
<th>Type, beskriv</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

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 bivirk, interaksjonsfare, mange medisiner allerede, ikke alvorlig familerisiko, pasientens holdning etc)
6) Har maks tilgjengelig 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_______
4) Bytter til svakere statin fra statin_______ til statin_______
5) Legger til ezetimibe
6) Legger til colesevamal
7) Legger til PCSK9-hemmer
8) Legger til Omacor
9) Legger til Niaspan
10) Legger til Inegy dose_______

Dato_______ Lege sign________________
**Pasienten har *ingen* lipidmedikasjon på visitt 3**

<table>
<thead>
<tr>
<th>Medikament ikke brukt</th>
<th>Grunnen til det</th>
<th>Avsluttet når dag/mnd/år</th>
<th>Fortsatt uten</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

**Pasienten har hatt lange *pauser* i lipidmedikasjon**

<table>
<thead>
<tr>
<th>Medikament ikke brukt</th>
<th>Grunnen til det</th>
<th>Pause start dag/mnd/år</th>
<th>Pause stopp dag/mnd/år</th>
<th>Fortsatt uten</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Barneønske/gravid/amming</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prosjekter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non compliant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annen sykdom</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**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

KE Arnesen Irene Mork
TTTFH
TTFH: Visitt 3

ADVERSE EVENTS

Ingen medisinske hendelser siden forrige visitt: □
Bruk helst diagnoser, ikke individuelle symptomer, hvis mulig

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Alvorlighet</th>
<th>Tiltak</th>
<th>Hvilken lipidmedisin ble gitt</th>
<th>Annet/opr etc</th>
<th>Do serious criteria apply?</th>
<th>Outcome, still present?</th>
<th>Årsak</th>
<th>Hvis nei, var årsaken Kardiovaskulær sykdom type:</th>
<th>Annet</th>
<th>Ansvarlig lege</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ 1 Mild □ 2 Moderat □ Alvorlig</td>
<td>□ 1 Øket □ 2 Redusert □ 3 Stoppet midlertidig □ 4 Stoppet permanent</td>
<td>□ Ja □ Nei</td>
<td>□ Ja □ Ukjent □ Nei- løst</td>
<td>□ Ja □ Ukjent □ Nei- løst</td>
<td>□ Ja □ Ukjent □ Nei- løst</td>
<td>□ 1 Ja, sannsynlig □ 2 Ja, mulig □ 3 Nei, usannsynlig □ 4 Nei, sikkert</td>
<td>□ Ja</td>
<td>□ Ja</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ 1 Mild □ 2 Moderat □ Alvorlig</td>
<td>□ 1 Øket □ 2 Redusert □ 3 Stoppet midlertidig □ 4 Stoppet permanent</td>
<td>□ Ja □ Ukjent □ Nei- løst</td>
<td>□ Ja □ Ukjent □ Nei- løst</td>
<td>□ Ja □ Ukjent □ Nei- løst</td>
<td>□ Ja □ Ukjent □ Nei- løst</td>
<td>□ 1 Ja, sannsynlig □ 2 Ja, mulig □ 3 Nei, usannsynlig □ 4 Nei, sikkert</td>
<td>□ Ja</td>
<td>□ Ja</td>
<td></td>
</tr>
</tbody>
</table>

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

KE Arnesen Irene Mork
TTT-FH
TTTFH: Visitt 3

SOSIAALT
Endringer siden forrige visitt: □ Ja □ Nei
Skoleelever □ Student/læringer □ 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 rokokt □ Tidligere rokokt □ Startet første gang_____ Sluttet siste gang_____
Sigarett rokokt □ Antall per dag_____
Pipe/cigarillos rokokt □ 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__________ □ Sterillisert

MEDIKAMENT ALLERGI □ Ja □ Nei
Hvis JA, hvilken prevensjon: Medikamentnavn/kasse Type reaksjon
__________________________________
__________________________________
__________________________________

KE Arnesen Irene Mork
TTTF-FH

4 av 5
<table>
<thead>
<tr>
<th>Potential Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Suspected or Confirmed Non Fatal Acute MI</td>
</tr>
<tr>
<td>☐ Hospitalization with Primary Diagnosis of CHF</td>
</tr>
<tr>
<td>☐ Death - Coronary</td>
</tr>
<tr>
<td>☐ Cerebrovascular Event</td>
</tr>
<tr>
<td>☐ Death - Other</td>
</tr>
<tr>
<td>☐ Fatal stroke</td>
</tr>
<tr>
<td>☐ Coronary Revascularization Procedure</td>
</tr>
<tr>
<td>☐ Non-fatal stroke</td>
</tr>
<tr>
<td>☐ Coronary artery bypass graft (CABG)</td>
</tr>
<tr>
<td>☐ TIA</td>
</tr>
<tr>
<td>☐ PTCA (includes athereectomy and stent implantation)</td>
</tr>
<tr>
<td>☐ First Diagnosis of PVD</td>
</tr>
<tr>
<td>☐ Other coronary revascularization procedure</td>
</tr>
<tr>
<td>☐ Hospitalized PVD Event</td>
</tr>
<tr>
<td>☐ Other Non-CHD Vascular Events</td>
</tr>
<tr>
<td>☐ Documentated Angina</td>
</tr>
</tbody>
</table>

Date of Event: [ ] [ ] [ ]

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: [ ] [ ] [ ]

Discharge Date: [ ] [ ] [ ]
Kjell-Erik Arnesen
Medisinsk klinikk

2014/753 Treat To Target Familært Hyperkolsterolæmi – Livsstil (TTT-FH - Livsstil)

Forskningsansvarlig: Oslo universitetssykehus HF
Prosjektleder: Kjell-Erik Arnesen


Vurdering

REK har vurdert følgende endringer i prosjektet:

2. Endre prosjektslutt fra 31.12.2016 til 01.01.2018

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

Vedtak

REK godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring under forutsetning av at ovennevnte vilkår oppfylles 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 dokumentasjonsensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal deretter slettes eller anonymiseres.

Opplysningene skal oppbevares aidentifieret, dvs. atskilt i en nøkkelen- og en datafil. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerthet i forskningsprosjekter innenfor helse- og omsorgssektoren».
Prosjektet skal sende sluttmelding til REK, se helseforskningsloven § 12, senest 6 måneder etter at prosjektet er avsluttet.

Klageadgang


Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Kopi til: ous@hfdl.no

Elin Evju Sagbakken
Seniorrådgiver