Morbidity, Mortality and use of Medication in Familial Hypercholesterolemia. A Registry Study.

1. Introduction

Familial hypercholesterolemia (FH) is an inherited disease charactherized by high plasma cholesterol, and this can lead to a high risk of premature cardiovascular disease (CVD) (1). It is estimated that approximately 15,000 people in Norway have FH and globally more than10 million people are affected (2). Cholesterol levels can be normalized in most patients by treatment. However, it is difficult to measure how this influence on hard endpoints such as heart attack or stroke. Placebo-controlled studies can not be conducted for ethical reasons. Thus, data are missing for answering questions about how modern treatment affects the prognosis for individuals with FH. In Norway there is a patient registry for all persons who are genetically diagnosed with FH. It is now the world's second-largest of its kind. We now have a unique possibility to link data from this registry to the central health registries in Norway. Hence, a large number of patients with this inherited disease can then be studied regarding causes of death, age-specific mortality, drug use, and various adverse events. In addition, possible effects of different mutations of FH can be studied.

2. Background of the project

FH leads to a high circulating low-density lipoprotein (LDL)-cholesterol and an increased risk of developing fatty deposits inside the arteries, atherosclerosis, and subsequently increased risk for CVD at a young age. Untreated, approximately half of men with FH will have CVD before age 50 years and about half of all women before the age of 60 (3). However, there is considerable variation in the age at which CVD occurs; some contracts CVD as early as 20 years of age while others are never affected. The frequency of FH is estimated to be 1:500 people globally (2, 4) but is slightly higher in Norway, 1:313 (5).

2.1. The genetics of FH

Three different genes can lead to FH. The most common are mutations in the gene encoding the LDL receptor. More than 1,100 mutations in this gene have been demonstrated worldwide (6). Approximately 135 of these have been found in people who live in Norway. Another cause of FH is a mutation in the gene for apolipoprotein B, which is the main protein in the LDL particle (7). This variant is uncommon in Norway. Very rarely FH can be caused by a mutation in the gene that codes for the enzyme PCSK9 (proprotein convertase subtilisin / kexin type 9) which is involved in the degradation of the receptor for LDL cholesterol (8). All these FH mutations results in increased LDL-cholesterol in the plasma from birth and increased risk of premature atherosclerosis in the vessel wall and in some cases to lipid deposition in other tissues, e.g. xanthomas in tendons, xanthelasms around the eyes and arcus cornea in the limb of the cornea. More than 5,000 patients are genetically diagnosed with FH in Norway. Based on gene frequencies more than 15,000 people have FH and the disease is still under-diagnosed.

2.2. The treatment of FH

A diet with a low content of saturated fat in combination with hydroxy-methyl-glutaryl-CoA reductase inhibitors (HMG-CoA reductase inhibitors, also called statins) normalize LDL-cholesterol in most patients with FH, notably if the drugs are well tolerated. Other drug

treatment can also be used. Ezetimibe is the most commonly used lipid lowering drug in combination with statins. Ezetimibe is a selective inhibitor of the absorption of cholesterol from the intestine. Another option is bile acid sequestrants (resins) which bind bile acids in the gut and inhibit re-absorption. Since cholesterol is the sole precursor of bile acids resins reduce LDL-cholesterol in plasma by increasing the demand of cholesterol for bile acid formation. Nicotinic acid also represents an option of treatment. Nicotinic acid inhibits the release of free fatty acids from adipose tissue, inhibits de novo lipogenesis and esterification of fatty acids to triglycerides in the liver so the plasma lipid profile improves.

2.3. Research tasks in this study

Task 1. Mortality in FH and how statin treatment affects the prognosis.
The modern treatment of FH is inadequately documented. It is commonly accepted that good control of LDL-cholesterol will reduce the risk for CVD (9). However, there is insufficient data on how this influence the risk associated with the FH. It is not known to what extent modern treatment normalizes life expectancy. People with FH are born with a high LDL-cholesterol which means that the vacular endothelium in the blood vessels will be exposed to high LDL-cholesterol for several years during childhood (1) before the patient start on drug therapy. This underlines the particular entity of FH. Results from large statin trials may not be directly applied to an FH population. There are, however, studies providing indirect evidence that lipid-lowering therapy has a positive effect on FH on for example plaque stability and intima media thickness (IMT) measured by ultrasound examination of central blood vessels (10-12).

Task 2. Use of medication in FH.
Usually, compliance of lipid-lowering treatment is not very high. Studies have found that about one third of those who started such treatment have ended after a year (13). In FH, there is a strong medical indication for the treatment, and compliance might be higher in these patients. However, from clinical experience we have learned that many individuals have stopped their medication for a variety of reasons. The lack of data on this issue is an obstacle to implement targeted measures to address the compliance issue.

Task 3. Lipid-lowering drugs and cancer.
It is unclear whether exposure to statins and other lipid-lowering drugs often used by FH patients such as ezetimibe and fibrates for a long period of time could be associated with the development of malignant diseases, such as colorectal cancer (14). On the other hand some studies suggest that statins may have a protective effect, particularly on the development of prostate cancer (15), breast cancer (16, 17) and esophageal cancer (18). Taken together, the bulk of evidence indicates that statins are not associated with cancer (19), and a very large meta-analysis disproved such a relationship for statins (20). However, the development of cancer is a slow process that will not necessarily be revealed during the five years most clinical trials last for. Consequently, even the largest meta-analysis is mostly based on studies of less than five years. Many FH patients have now used statins for twenty years or more. No other patient groups have used lipid-lowering drugs such a long period of time.

Task 4. Knowledge about lipid lowering drugs in pregnancy.
Pregnant women need to stop lipid-lowering medication and pregnancy by it self increase the plasma lipids. Thus, LDL-cholesterol increase by 2-3 folds during pregnancy in FH. Pregnancy, lactation and time trying to get pregnant can collectively represent many years of women's lives. Statins are contraindicated during this time. The present lack of data represents a problem when advising these FH patients what to do with regard to treatment. It is important to gain

knowledge about the risk for CVD and any adverse pregnancy outcomes. In a pilot study of the present project we successfully used registry data to conclude that women with FH did not deliver preterm (21, 22). In the present project we plan to expand and the registry links and thus generate more detailled information about this issue.

Task 5. Knowledge about morbidity in FH and the consequence of long term statin.
Morbidity in FH have been studied in the Simon Broome registry study (23, 24), but the present study will be larger and will generate updated information. It is likely that the general morbidity has changed by time, since more patients have used statins for a longer period. For example, the effect of statin treatment has been studied for no more than two years in children with FH in clinical trials (25, 26). There is little knowledge of longer treatment, representing a problem since statins competitively inhibit the regulatory step in the endogenous cholesterol synthesis. Cholesterol is the biochemical foundation of all steroid hormones, including sex hormones. Some studies have found that statins affect the gonads (27) and erectile dysfunction (28, 29). However, many children from 8 years and above have now been treated with statins for years (30). Registry data allows us to investigate whether these children have continued their medication and whether they have been hospitalized or medically treated for any other diseases that could be related to treatment of statins during the years.

Task 6. Detailled knowledge about CVD in FH and the effect of long term statin treatment.
Clinical trials have provided good evidence on the lipid-lowering effect of treatment in FH and are supported by studies on the intima media thickness (12). However, there is little data on hard endpoints. The treatment of FH is empirically well grounded on the assumption that a normalization of LDL cholesterol will reduce the risk for clinical events. However, evidence based data on hard end points are insufficient. It is therefore important to obtain better data on the incidence of CVD in the FH population, including the relation to current use of medication.

2.4. The Patient Register for individuals with FH in Norway at the Medical Genetic Laboratory, Oslo University Hospital, Rikshospitalet (MGL).

MGL was established in 1998 and it contains information on gender, age, mutation type, cholesterol value at the time of diagnosis and cholesterol value before starting cholesterol-lowering medication. It also contains information about height, weight, age at initiation of medication, presence of hypertension or CVD and tobacco use. MGL identifies the person by the unique national registration number assigned to all Norwegian residents and it can therefore connect tobe merged with other health registries. All individuals with genetically verified FH in Norway are registered in the MGL and therefore MGL is expected to be fully representative of the FH population in Norway. Blood samples are sent to MGL from across the country. There are 2509 men and 2676 women registered in MGL as of August 25, 2011. By dividing this population age-wise in quintiles 1/5 is born before 1951, 1/5 is born between1952-1963, 1/5 is born between 1964-1974, 1/5 is born between 1975-1987 and 1/5 is born between 1988 and 2011. All patients have given their signed consent for genetic testing.

2.5. Important research challenges in FH that can not be addressed by large clinical trials

It is practically impossible to organize a sufficiently large clinical trial to study hard endpoints in FH. A trial on hard end-point would require thousands of FH patients being treated for several years before one can expect measurable impact on heart attack, stroke and mortality and without a placebo group the results will not be conclusive. Hence the proposed registry-project represents a highly relevant alternative to explore the epidemiology of FH.

3. The purpose of the study

3.1. The Overall Objectives of the project

The overall goal is to provide the best possible description of key health and to discuss this knowledge in relation to the major health challenges that are associated with FH. Such knowledge may contribute to better health among FH patients. This project will particularly ddress six tasks in FH, as described in the background and listed in table 1.

Table 1. Tasks of the Project and Registries that MGL will be linked with

	Research questions:	MGL will be linked with:
T1	Mortality in FH	Cause of Death Registry and NorPD
T2	Use of Medication in FH	NorPD
T3	Incidence of Cancer in FH	The Cancer Registry of Norway and NorPD
T4	Lipid lowering drugs in Pregnancy and the outcome of pregnancy and birth in FH	The The Medical Birth Registry of Norway and NorPD
T5	Causes of hospital admissions in FH	The NPR / The National Cardiovascular Registry
T6	Incidence of CVD in FH	The NPR/ The National Cardiovascular Registry

3.2. About the health registers that MGL will be linked with in this study

Cause of Death Registry
Death certificates are collected by the Cause of Death Registry for coding of information based on an international system and determines the cause of death to be used in the cause of death statistics (underlying cause of death). The register allows us to follow developments in mortality e.g. for heart attacks, cancer, accidents and suicide. The register is dating back to 1853, based on doctors' reports but it has been changed and improved several times since then.

The Norwegian Prescription Database (NorPD)
The NorPD contains a complete overview about dispensing of prescribed medicines to patients, doctors and institutions from pharmacies. The NorPD was established in 2004. Drugs purchased without prescription are not included.

The Medical Birth Registry of Norway (MBRN)
For all births in Norway, the midwife / doctor sends a notification of the birth to the MBRN. Since 1967 information about all births in Norway has been collected in this registry, including stillbirths after 12 weeks of pregnancy. Maternal health conditions before and during pregnancy, and any complications experienced during pregnancy or at birth as well as information about the newborn baby's health are recorded.

The Cancer Registry of Norway
The Cancer Registry of Norway was established in 1951 and is one of the oldest of its kind in the world. All cases of cancer in Norway have been reported to the Cancer Registry from 1 January 1952, due to an Act on physicians' rights and obligations in Norway.

The Norwegian Patient Register (NPR)
NPR contains information on all patients waiting for or has been treated within the specialist health service. The registry was established in 1997. Data up to and including 2007 are not

personally identifiable but may be linked to individuals within the same institution and calendar year. In February 2007, the Parliament (Stortinget) decided to establish it as a person-encrypted Norwegian patient registry. Most of the information in the NPR can be categorized as administrative information. These are: Reference time and priorities, location (institution), care level (outpatient, day or inpatient treatment, hospital admission), date and time of treatments, planned or emergency, where the patient was discharged to, time of discharge, referral and diagnoses (ICD-10), the NOMESCO Classification of Surgical Procedures (NCSP) and Norwegian Classification of Medical Procedures (NCMP).

The National Cardiovascular Registry

The Norwegian Parliament adopted 22 March 2010 to create a national registry of cardiovascular disorders. In August 2011 the Health and Care Ministry will send a proposal for regulation on the establishment of a national cardiovascular registry. This registry will, most importantly, contain patient status, diagnosis, treatment, length of stay in hospital, readmission, rehabilitation and functional measures. At present there is no guarantee that this registry will be available for use in the present project. The decision to establish the registry has, however, been taken, and if it is possible to use it within the next 2-3 years it will be of great interest for the present study. However, the present project does not depend on this registry.

4. Implementation of the project

4.1. Planned activities

- The causes of death in patients with FH in Norway will be identified. Mortality trends over time will be studied. The effect of modern treatment will be evaluated by discussing mortality and morbidity in the perspective of old data.
- By the link between the NorPD, the MBRN and MGL we can track how many women who were prescribed medication in the period they were pregnant. This shall be related to pregnancy outcomes such as birth weight and gestational age and the incidence of congenital malformations. The use of lipid-lowering medication in the first, second or third trimester may be important in relation to pregnancy outcome. This may allow us to conclude on the eventual risk of using statins during pregnancy. We will also study if the use of statins may be associated with the fertility rate in a FH population.
- We will describe the use of drugs, in particular the use of lipid-lowering drugs from the NorPD. We will identify the incidence of various cancers and any eventually associations with the number of years on lipid-lowering medication. We will investigate whether early initiation of statin therapy in childhood is positively or negatively associated with health parameters registered in the central health registers. Any associations with FH mutation type will be investigated. Data to be collected from the various registries are summarized in table 2.

Table 2 Data to be collected from the respective health registers

Cause of Death Registry	Cause of death Date of death Death in or outside hospital
The Cancer Registry of Norway	Date of diagnosis Localization Histology Cancer stadium
NorPD	Type dispensed drugs Dose of dispensed drugs Date of delivery of drugs

The MBRN	Use of drugs in pregnancy Interventions/measures during labor Complications during childbirth Complications in the mother after birth Congenital malformation
NPR	Referral and diagnoses (ICD-10) Surgical procedures (NCSP) Medical procedures (NCMP)
The National Cardiovascular Registry	Diagnosis (ICD-10) Treatment (NCSP/NCMP) Length of stay in hospital Rehabilitation/functional

4.2. Time frame

Application for permission to link FH patient regiser to mortality data is sent. Application to the IEC for the link to the mortality data was submitted to the IEC 10 May 2011. The time schedule and publication plan is summarized in table 3.

Table 3 Work schedule and publication plan

2011-Q2	Application Ethics, Helse Sør-Øst, the Data Inspectorate and University of Oslo
2011-Q2	Masterstudent start working
2011-Q3	Submission of application to The Norwegian Institute of Public Health of MGL to Cause of Death Register
2011-Q3	Application Ethics and the Data Inspectorate for the link between MGL and the regsiters other than the Cause of Death Register
2011-Q4	Training of masterstudent in methodology and statistics
2011-Q4	Announcement for a Research Fellow/PhD student
2012-Q1	Raw data from The Norwegian Institute of Public Health regarding the linking og MGL to the Cause of Death Register is expected to be ready.
2012-Q1	Letter with Consent is sent out to all people in the FH register
2012-Q1	Written consent is registered
2012-Q2	Masterstudent start working on the statistics on data from the Cause of Death Register
2012-Q2	Training of PhD student in methodology and statistics
2012-Q2	Informed Consent period is closed
2012-Q3	Raw data from The Norwegian Institute of Public Health regarding the linking og MGL to other registers than the Cause of Death Register is expected to be ready.
2012-Q3	Anaysis of data from linking MGL to other registers than the Cause of Death Register starts
2012-Q3	The masterstudent will finish his examination
2012-Q4	Submission of the first paper: Mortality in FH
2013-Q1	Submission of the second paper: Use of medication in FH
2013-Q3	Submission of the third paper: Incidence of cancer in FH
2014-Q1	Submission of the fourth paper: Lipid lowering drugs in pregnancy in patients with FH in relation to birth outcome
2014-Q3	Submission of fifth paper: Causes of hospital admissions and Incidence of CVD in patients with FH
2014-Q4	PhD thesis is to be submitted

The masterstudent will have a major role in paper one. The PhD student will have a major role in paper two to five. The fifth paper will partly depend on a successful establishment of The National Cardiovascular Registry. The PhD student will be first author on three papers and a co-author of one.

4.3. Statistics

Mainly two types of analyses will be conducted. 1) The risks of the specified endpoints in FH patients will be compared with the risk in the general population, taking age and sex into account. The standardized incidence ratio or standardized mortality ratio will be used for these external comparisons. 2) Analyses of incidence and mortality of the specified endpoints in the FH registry patients and the relation with the specified risk factors. Kaplan-Meier curves and multivariable Cox regression will be used.

4.3.1. Study sample and expected number of endpoints: The study sample consists of ~5000 FH patients in MGL. There has been a gradually annualincrease in the size of MGL from 1998 to 2011 giving ~32,900 person years of follow-up through 2010.

4.3.2. Total death and CHD deaths: The FH patients in the present study are comparable to the Simon Broome Register data (23, 24) as regards age and sex. Here, a total of 73 deaths including 46 coronary heart disease (CHD) deaths were observed during a total of 8770 person years. Assuming the same mortality in MGL as in the Simon Broome Register, we expect 274 deaths, including 172 CHD deaths in the present study.

4.3.3. CHD incidence: The 1-year mortality following CHD for persons under 80 years was found to be 9.3% in Sweden (33). The expected number of CHD events in the present study is a total of 1855, as calculated from the expected 172 CHD death and a mortality of a 9,3%.

4.3.4. Cancer incidence: The estimated mean age in MGL given in quintiles is: 12 year, 30, 42, 54 and 74, respectively. A previous study from the Simon Broome Register reported that the standard mortality ratio (SMR) from all cause cancer in FH was 0.96 (24). We assume that the cancer incidence in the present FH population is equal to that of the general population in Norway. We then used the age-specific incidence rates for all cancers in Norway in 2005-2009 (32). Using the age quintiles in MGL and assuming that the 2509 men and 2676 women were equally distributed in the age groups the expected incidence of all cause cancer were according to table 3. I have participated in Courses in administration and management, and I have had the responsibility for 10-14 persons as head of section for clinical trials on Lipidklinikken in the period 2000-2009.

Table 3 Expected incidence of all cause cancer in 2011

Age (yr)	*12*	*30*	*42*	*54*	*74*	*SUM*
Women	1	6	14	31	42	94
Men	1	3	5	14	95	117
Total	1	9	19	45	138	211

The table applies only to year 2011. For the entire period of MGL from 1998-2011 the number is more than six times higher. Because we p.t. not have the exact age and sex distribution of population throughout the period, only figures for 2011 is presented.

4.4. Measures to preserve and protect the participants in the project

A data file with a list of people with FH will be handed over to the computer responsible person at the Norwegian Statistics. This data file will then be connected to NorPD and the Cause of Death Register in accordance with applicable regulations and procedures. Similarly, the delivery made to the Cancer Registry and the Directorate of Health for the link to the NPR. The aggregate numbers that are the result of the links will contain the mutation type, lipid profile, where appropriate, age and gender and no aggregate figures with n <10 will be analyzed to ensure that the information not to be attributed to any individual. No information can be used to identify any individuals.

4.5. Self-assessment of innovation potential of the project

The combination of the large number of FH patients in MGL and the possibility to link data to central health registries offers a unique opportunity that can only be done in Norway at present. Many FH patients worry about their risk for premature CVD despite current treatment. Data from this project will add knowledge to this question. The project will provide unique information about long-term use of lipid-lowering drugs in relation to cancer, as well as long-term data on treatment of children and pregnancy outcome. It will have a socio-economic impact because it helps to evaluate the effect of treating FH and will thereby help to enable cost-benefit calculations in relation how much it costs to track more of the estimated 10,000 people with FH, still undiagnosed in Norway.

5. Previous fundings

The project leader have received NOK 50,000 from Throne Holst Foundation for Nutrition Research.

6. Project management

Project leader is Kjetil Retterstøl. Position: Associate Professor/ Consultant: Lipid Clinic, Oslo University Hospital and Department of Nutrition, University of Oslo. Work Address: PO Box 1046 Blindern, 0317 Phone: 22 85 15:21 Phone: 900 98393. E-mail address: kjetil.retterstol@rmedisin.uio.no. Role: supervisor for the students.

Table 4 Project Management

Name	Position	Role
Per Ole Iversen	Prof., Nutrition, UiO and Consultant Internist, OUS	Co-Investigator
Trond Leren	Consultant Geneticist, Unit for Cardiac and Cardiovascular Genetics, OUS	Co-Investigator
Leiv Ose	Prof.Nutrition, UiO, and head of the Lipid Clinic, OUS	Co-Investigator
Kjetil Retterstøl	Associate Prof., Nutrition, UiO, and Consultant MD at the Lipid Clinic, OUS	Principal Investigator
Mirza Sarancic	Masterstudent	Masterstudent
Marit Bragelien Veierød	Professor at the Department of Biostatistics and Nutrition	Co-Investigator

Iversen is a Consultant Internist and Professor in clinical nutrition. This combination will be of immense value in this project. He has a relevant track record in both basic projects and intervention studies and has supervised several PhDs. He will act as co-supervisor and contribute actively in data analyses and writing of manuscripts.

Leren is a Consultant Geneticist and founder and head of Unit for Cardiac and Cardiovascular Genetics at Oslo University Hospital. Since the 1980s, he has had a special focus on the molecular genetics of FH and other genetic lipid disorders. Together with Dr. Ose, he has been the architect behind the molecular genetic program to diagnose FH in Norway. He also directs a research program to study cellular lipid metabolism and his contribution is invaluable for this project. He has supervised several PhDs and published many relevant articles.

Ose is Consultant in Pediatric, Professor in Nutrition and head of the Lipid Clinic which he founded in 1989. Treatment of FH have been his main focus since the early 1980's and he is the most experienced doctor in this field in Norway. His overall understanding of the disease will be of immense value in this project. He has supervised several PhDs and he has published a large number of relevant articles.

Retterstøl is a Consultant at the Lipid Clinic and Associate professor in Nutrition. He has 20 years of clinical experience with treatment of FH. He is a specialist in clinical chemistry. He headed for several years the clinical trials unit at the Lipid Clinic and he has been the responsible MD at the section for drug monitoring in the Norwegian Medicines Agency. He will lead the project and act as the main supervisor for the master student and the PhD student.

Veierød is Professor at the Department of Biostatistics and Nutrition. She has 20 years of experience in supervising in research methods and statistical analysis in medicine and health science. She has supervised several PhDs and her track record is relevant. Her specialty covers measurement errors, missing data and other possible sources of error in epidemiological studies. Her research focus is on lifestyle factors and risk of cancer and CVD and will be of particular importance in the present study.

Sarancic started on the mortality project in July 2011 as his masterstudy.

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