Phenotypic characterization of patients with familial hypercholesterolemia

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Abstract

Background
Autosomal dominant hypercholesterolemia (ADH) is known to be a major risk factor for cardiovascular disease (CVD), in particular coronary events. Familial hypercholesterolemia (FH) is the most common cause of ADH. This disorder is characterised by high levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). FH is the result of mutations in the genes coding for the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 (PSCK9). However, in a substantial proportion of patients with a clinical phenotype of FH no mutation can be detected. In the present study we assessed potential acquired causes of FH in FH mutation negative patients and evaluated the cardiovascular risk in patients and relatives with and without mutations.

Methods
This retrospective study included 347 patients with a clinical phenotype of FH. All patients were outpatients from the University Medical Center Groningen (UMCG). Genetic analysis was performed in 337 patients, after informed consent. Patients lipid values, cardiovascular events, acquired causes of dyslipidemia, family history of CVD and hypercholesterolemia, and the results of the genetic tests were obtained using the digital patient database of the hospital. These data were compared between the patients with a FH related mutation (FH+) and the patients where no pathogen mutation could be identified (FH-).

Results
In total there were 127 FH+ patients (37.7%) and 210 FH- patients (62.3%), while in 10 patients the genetic test results could not be retrieved. The mean age was 47.6 years. FH-patients were significantly older, and more frequently had hypertension. The prevalence of cardiovascular events, in particular myocardial infarction was higher in the FH- patients. While more family members of FH+ patients also had high cholesterol, more first-degree relatives with FH- had CVD. None of the acquired variables for FH significantly differed between FH- and FH+ patients. Many FH+ and FH- patients did not reach target LDL-C levels of <2.5 mmol/l with statins.

Conclusions
No genetic mutation can be detected in 60% of the patients with clinical suspicion of FH. In these patients, no potential acquired cause of FH could be identified, which points to a possible polygenetic cause of high cholesterol levels. Interestingly, FH- patients and their first degree relatives were at higher risk of cardiovascular events, in particular myocardial infarction. Therefore, stringent cardiovascular control and treatment in FH- patients is as important as in FH+ patients.
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**Introduction**

Familial hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism, characterized by elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in plasma, which is transmitted in an autosomal-dominant manner (1). Long-term cholesterol elevation deposits in the tissues, which causes external manifestations, such as tendon xanthomas, xanthelasmas and corneal arcus. These high levels of cholesterol are associated with an increased risk of premature cardiovascular events, in particular coronary heart disease (CHD) (1-3).

The prevalence of heterozygous familial hypercholesterolemia (heFH) is estimated to be 1 in 300-500 individuals in most European countries (1-3), although this might be an underestimation in certain populations in which a founder effect occurs (4). heFH is the result of loss-of-function mutations in one allele of the low-density lipoprotein (LDL) receptor gene. These mutations negatively affect the rate at which LDL-C is cleared from the blood, due to a lack of functional hepatic receptors for the uptake of circulating LDL. Mutations in both alleles of the LDL receptor gene result in homozygous familial hypercholesterolemia (hoFH). hoFH has an estimated prevalence of 1 in 1 million persons. The cholesterol levels are extremely high in hoFH patients, because of the near total or total loss of LDL receptor functionality (1).

In most Western countries less than 10-15% of people with FH are diagnosed, while this is 20% in the Netherlands (5,6). The higher percentage in the Netherlands is the result of a cascade screening program since 1994 (7,8). However, most people with FH are undiagnosed or only diagnosed after their first coronary event.

FH patients have an increased lifetime risk for cardiovascular disease (CVD). Asymptomatic middle-aged FH patients have significantly higher atherosclerotic burden than controls, which is associated with a family history of premature coronary artery disease (9). If FH remains untreated, affected males have approximately 50% chance of experiencing a fatal or nonfatal coronary event before the age of 50 years, and this is at least 30% in females by the age of 60 years (2,3). The atherosclerotic burden in FH begins in childhood, indicating the need of early identification and preventive measures (10). Half of the children with high concentrations of TC and LDL-C will have elevated lipid levels in adolescence and early adulthood, so identification and treatment in certain populations of adults may prevent coronary heart disease (11).

**Genes involved**

FH is caused by mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), and proprotein convertase subtilisin/kexin type 9 (PSCK9) genes (12).

**LDLR**

Loss-of-function mutations in the LDLR are in the vast majority of FH patients the underlying molecular defect. Approximately 93% of the identified mutations are in the LDLR (13,14). Many different types of LDLR mutation have been identified in patients with FH worldwide and many mutations are population specific. Most populations have a number of mutations that leads to the FH phenotype.
APOB
Around 5% of FH patients have a mutation in APOB (13,14). This is the major apoprotein component of LDL-C that acts as a ligand for the LDLR. Mutations in the gene coding for APOB also reduce LDL clearance, resulting in the disorder known as familial defective apolipoprotein B (FDB), which is clinically indistinguishable from FH. FH, FDB and inherited hypercholesterolemia of unknown aetiology are commonly referred to as autosomal dominant hypercholesterolemia (ADH).

PSCK9
2% of the patients with FH have a mutation in PCSK9, which is a protein involved in the degradation of the LDLR (13,14). Mutations in PCSK9 have also been shown to be a rare cause of ADH.
PSCK9 mutations can affect the phenotype in different ways, either gain of function or loss of function mutations (12). Gain of function mutations are associated with decreased LDLR on the surface, causing ADH (15). Loss of function mutations on the other hand are associated with decreased LDL-C levels and protection from CVD (16,17).

Diagnosis of FH
Serum TC ≥240 mg/dL (6.21 mmol/l) and LDL-C ≥160 mg/dL (4.14 mmol/l) are classified as high (18). In FH patients the high-density lipoprotein (HDL) levels are within the normal range (or low), so the diagnosis is made using LDL-C levels.
Although most patients with FH have very high LDL-C concentrations, this is not the case in some patients. In a number of patients with a mutation in the LDL-R, LDL-C levels between 4.0 and 6.5 mmol/l can be found. Genetic tests are therefore always necessary to confirm the diagnosis.
In some patients with FH, abnormal concentrations of triglycerides and/or HDL cholesterol (HDL-C) can be found, however these findings usually have their origin in secondary causes.

FH can be diagnosed either clinically or genetically, however usually a combination of clinical criteria and genetic testing is used (19). There are three well-defined criteria for diagnosing FH (20,21). These include the US Make Early Diagnoses Prevent Early Deaths Program Diagnostic Criteria (MEDPED) (21,22), which is shown in appendix 1. The second set of criteria is the Simon Broome Register Diagnostic Criteria (21,23), shown in appendix 2. And the third set of criteria is the Dutch Lipid Clinic Network Diagnostic Criteria (21,24), shown in appendix 3. MEDPED focusses on LDL-C levels and family history. The Simon Broome Register and Dutch Lipid Clinic Network criteria both use a combination of LDL-C levels, physical findings, family history, clinical history and DNA analysis for the diagnosis of FH.

The normal cholesterol values in children are significantly lower than in adults. When a clearly increased LDL cholesterol concentration is found in a young child, the diagnosis of FH can be confirmed, since this high level can only be the result of FH, simply because either the mother or the biological father also has FH.

Genetic screening
Genetic screening is important due to the fact that FH is an extremely common metabolic disorder, affected patients die from the disease if untreated and highly effective treatment is available. Genetic testing is essential for screening and diagnosis of FH patients (25). Some countries such as the Netherlands, Spain and Wales have a long-standing and organized
program with an active community approach (26). In the Netherlands, the Foundation for Tracing Hereditary Hypercholesterolaemia (StOEH) was founded in 1994, with the main goal of tracing patients with FH in order to start early treatment (27). The basis of this screening program consists of genealogical research and DNA diagnostics. The identification of gene mutations in the Netherlands was performed in the Academic Medical Centre (AMC) in Amsterdam, while cooperating with the StOEH. Since 2010, mutation analysis in patients with a high risk of having FH can also take place at the UMCN. First, DNA is analysed for the presence of mutations in LDLR; the majority of FH patients have a mutation in this gene. When no mutation can be found, APOB and PSCK9 are also tested.

Once an individual with a genetic diagnosis of FH is identified, the strategy of cascade screening allows identification of family members of these index cases by using the inheritance pattern across the pedigree (20,28,29). Cascade screening is a straightforward and highly effective way to identify persons who have FH and therefore are at risk of early CHD (30,31). When the family of an affected patient is screened, often several additional affected family members are identified, because the genetic abnormality is an autosomal trait with complete penetrance. The screening program is primarily designed for adults, although screening in children is discussed with the parents. Children are often tested, because FH is clinically evident from birth; however follow-up of children with FH after diagnosis established through cascade screening could improve (32).

Despite advances in DNA analysis technology, there are clinically diagnosed FH patients in whom no mutation in the LDLR, APOB and PCSK9 genes can be found, which therefore does not result in a molecular diagnosis (33). With the current molecular diagnostic techniques, a FH-causing mutation can be found in ~40% of FH patients who are tested (14). Classified by the presence of tendon xanthomas, a FH-causing mutation can be detected in 20-30% of patients without tendon xanthomas and in 60-80% of patients with tendon xanthomas (14).

This suggests the existence of additional mutations in other (unknown) genes that can cause ADH, which needs further research (34). It is also possible that in a proportion of patients with a clinical diagnosis of FH a polygenic cause may be present, due to the inheritance of multiple common LDL-C-raising alleles (each of modest effect) leading to elevation of LDL-C above the diagnostic cut-off (35).

Secondary causes of high LDL

There are multiple secondary causes of hyperlipidemia, which always need further evaluation. The most common conditions are diabetes mellitus and excessive alcohol intake (36). Some of the secondary causes are associated with high LDL-C levels and therefore result in a higher risk of CVD. Secondary causes of high LDL-C include hypothyroidism, type 2 diabetes mellitus (DM), nephrotic syndrome, chronic renal failure, obesity and drugs.

Hypothyroidism

Subclinical hypothyroidism is a common condition, defined by high levels of thyrotropin-stimulating hormone (TSH) and affecting millions of people around the world. Hypothyroidism most typically raises LDL-C, but hypertriglyceridemia can also be seen. The severity of the lipid abnormalities increases with the severity of the hypothyroidism (37). Subclinical hypothyroidism is also frequently associated with hyperlipidemia, but also with arterial hypertension, and CVD. The risk of CVD is significantly increased in patients with mild subclinical hypothyroidism younger than 65 years (38).
Type 2 diabetes mellitus
Hyperlipidemia associated with insulin resistance is common in patients with type 2 DM (39). Type 2 DM is associated with moderate elevation in triglyceride levels and low serum HDL cholesterol values. The lipoprotein abnormalities are related to the severity of the insulin resistance. Type 2 DM is associated with a marked increased risk of CVD (40).

Nephrotic syndrome
Hyperlipidemia can occur in the nephrotic syndrome primarily due to high serum TC and LDL-C concentrations.

Chronic renal function
Dyslipidemia is less prominent in chronic kidney disease (CKD), but CKD is associated with elevations in LDL-C and triglycerides, and low levels of HDL cholesterol.

Obesity
Obesity is associated with a number of changes in lipid metabolism. These are high serum concentrations of TC, LDL-C, very low-density lipoprotein (VLDL) cholesterol, triglycerides, and a reduction in serum HDL cholesterol concentration (41). Loss of body fat can reverse the hypercholesterolemia and hypertriglyceridemia.

Drugs
A number of medications (e.g. thiazide diuretics, beta blockers, and oral oestrogens) can modestly affect serum lipid concentrations, either directly or through effects on weight or glucose metabolism.

Treatment
When it comes down to treating FH patients, healthcare professionals should follow European Atherosclerosis Society (EAS) guidelines (42). First step in an attempt to lower LDL-C and reduce CVD risk factors, are lifestyle modifications. These are the cornerstone for reducing the risk of CVD and include achieving and maintaining a healthy body weight through exercise and appropriate diet, restriction of alcohol consumption and smoking cessation. However, the effects of lifestyle intervention on LDL-C are modest and variable but may positively influence CVD risk factors and are therefore always recommended (43). Other secondary causes of dyslipidemia and CVD risk factors should always be controlled and treated aggressively. Lifestyle modifications are rarely, if ever, sufficient to achieve LDL-C goals in patients with FH and drug therapy is therefore required in almost all patients (44). Statins have shown to safely and effectively lower LDL-C levels (45), which delays the onset of cardiovascular events and make statins the first-line therapy of choice in patients with FH (46). In the case of severe heFH and hoFH, more intensive treatment and alternative therapeutic approaches are needed for these high-risk patients (47,48). When patients are diagnosed with FH, European and Dutch guidelines recommend treating LDL-C to plasma goal levels of <2.5 mmol/l (18,49), with an alternative treatment goal of >50% LDL-C reduction, as recommended in the NICE guidelines (19). Unfortunately, many FH patients do not reach target LDL-C goals with statins (6,50). Although statin treatment is widely used treating FH patients, many patients require alternative medication, such as patients that have side effects of statin therapy or those that cannot reach treatment goals (51,52).
Children
Early treatment with statin therapy in children delays the progression of carotid intima-media thickness (IMT) in adolescents and young adults. Treatment with statins in children with FH thus might be beneficial in the prevention of atherosclerosis in adolescence (53), although few patients were able to reach low LDL-C levels (54).

PSCK9 inhibitors
In recent years more and more therapeutic approaches have been developed for FH patients who do not reach target LDL-C levels. One of the most promising and effective new compounds for FH are the PCSK9 inhibitors (55,56). Recent studies have shown that PCSK9 inhibition is very effective in reducing LDL-C levels (57,58). When added to atorvastatin, short-term PCSK9 inhibition safely reduces LDL-C by 40% to 72% (59). Future studies are needed to test prolonged use (60). The beneficial effects of PCSK9 inhibition on LDL-C levels will hopefully translate into cardiovascular risk reduction in future phase III trials (61).
Aims of the study
The research aims of this study are:

1. Identification of acquired ADH in patients without known mutations in the default FH causing genes (LDLR, APOB, PSCK9).
   - Inventory of the current database of patients with ADH
   - Identification of patient characteristics (e.g. blood lipids, family history, events)
   - Inventory of the mutation analysis results

2. Analysis of the cardiovascular disease penetrance in families with and without FH-related mutations.

Hypotheses
The corresponding hypotheses for this study are:

1. Acquired causes of high LDL-C levels in patients with ADH, without a mutation in LDLR, APOB and PCSK9 are more prevalent than in patients with FH mutations.

2. Patients with FH mutations and their family members have higher LDL-C levels, and are therefore at higher risk of CVD compared to patients without FH mutations.

Relevance
Since there are many individuals with a FH phenotype where no mutations can be found in the default FH causing genes, there must be other causes of high LDL-C levels. As these high LDL-C levels are associated with an increased risk of cardiovascular events, it is important to study and assess these causes, in order to prevent or treat them in the future.
Methods

Study group
The included patients in this study were patients with a high clinical suspicion of FH visiting the lipid outpatient clinic of the UMCG. The clinical suspicion was based on elevated LDL-cholesterol values, physical examination, positive family history of CVD or hypercholesterolemia, or a clinical history of CVD. Another major reason for a high suspicion of FH in a patient was a known family member with FH, with an indication for cascade screening. DNA analysis was performed in patients who gave their informed consent. Blood was sent to the DNA laboratory of Vascular Medicine of the AMC in Amsterdam. Since 2010, DNA analysis for FH is also performed in the UMCG. Of the 347 patients in this study, 338 were genetically analysed. DNA analysis was not performed in the remaining 9 patients, either since the patient did not consent or the patient was too young. The UMCG investigated 125 patients, and the remaining 213 patients were tested earlier in the AMC, Amsterdam. In one patient DNA analysis was performed, however the results of the genetic tests were unknown.

Data collection
Data from the included population was obtained using the digital patient database from the hospital (Poliplus). The data consisted of patient lipid values, secondary causes of high LDL-C (hypothyroidism, type 2 DM, nephrotic syndrome, chronic renal failure and obesity), other risk factors for CVD (cigarette smoking and hypertension), cardiovascular events, family history of CVD and hypercholesterolemia, and the results of genetic testing.

The secondary causes of high LDL-C were extracted in the form of thyroid stimulating hormone (TSH), diabetes status, urine investigation (micro albuminuria/proteinuria), estimated glomerular filtration rate (eGFR) and body mass index (BMI). Other risk factors for CVD were also extracted. These included hypertension and smoking habits. Hypertension is defined as systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg and smokers are included at the time of the study.

The current database of patients with a FH phenotype was analysed and supplemented using the extracted data.

Cardiovascular events
Cardiovascular events included cardiovascular death, nonfatal myocardial infarction (MI), cerebrovascular events (stroke, transient ischemic attack or intracranial hemorrhage), angina, heart failure, and peripheral arterial disease.

Acquired causes of dyslipidemia
This study included hypothyroidism, type 2 DM, nephrotic syndrome, chronic renal failure and obesity as secondary causes of high LDL-C. All these causes were extracted using either patient files or laboratory results.

Hypothyroidism was defined as TSH values above 4.0 mU/L. Normal range for serum TSH is about 0.5 to 3.9 mU/L.

A positive type 2 DM was defined as a non-fasting glucose concentration ≥11.1 mmol/L or a fasting plasma glucose at or above 7.0 mmol/L.

Nephrotic syndrome was defined as proteinuria of more than 1 gram per 24 hours.

Chronic renal failure was defined as an eGFR below 60 mL/min per 1.73 m2. Albuminuria was also assessed since this is a marker of kidney damage. The albumin-to-creatinine ratio is widely used with a threshold for an abnormally elevated ratio of 3.4 mg/mmol or greater.
Obesity was evaluated using BMI which is the most practical way to evaluate the degree of obesity. Obesity is defined as a BMI of 30 kg/m2 or greater.

**Family history**
The family history consisted of CVD below the age of 60 and hypercholesterolemia, both in first and second degree family members. 
First-degree family members with premature CVD were parents, brothers, sisters and any children. Premature CVD were cardiac, cerebrovascular or peripheral vascular problems before the age of 60 years. 
First-degree family members with hypercholesterolemia were parents, brothers, sisters and any children. Hypercholesterolemia had no age limit. Hypercholesterolemia was defined as TC ≥6.21 mmol/l and LDL-C ≥4.14 mmol/l (18), although the StOEH uses a cut-off point of TC ≥5 mmol/L ([www.stoeh.nl](http://www.stoeh.nl)). Whenever a specialist referred to hypercholesterolemia or high cholesterol in family members, these values were maintained.

Second-degree family members with CVD were grandparents, grandchildren, uncles, aunts, nephews and nieces. Premature CVD were cardiac, cerebrovascular or peripheral vascular problems before the age of 60 years. 
Second-degree family members with hypercholesterolemia were grandparents, grandchildren, uncles, aunts, nephews and nieces. The definition was the same as in first-degree family members with hypercholesterolemia.

**Genetic tests**
The gold standard for FH diagnosis is demonstrating the presence of a mutation responsible for the defective function of the LDL receptor.

The main criteria for genetic analysis are:
- The patient has 6 or more points according to the score table (appendix 3)
- The patient has xanthomas, which occurs on a minority of FH patients,
- Or, the patient is a child (<17 years) with a LDL-C above 95th percentile for age and gender (>3.5 mmol/l for children under 17 years),
- Or, the patient has possible FH and a child (<17 years) with a LDL-C above 95th percentile for age and gender (>3.5 mmol/l for children under 17 years).

When these criteria were met, 10 ml blood [with ethylenediaminetetraacetic acid (EDTA), which prevents the blood from clotting] was sent to the laboratory for diagnostic sequencing. DNA was isolated from 5 cc of blood using a DNA-extraction device (AutopureLS from Gentra Systems). The analyses were performed using diagnostic sequencing. An advantage is that the entire gene is analysed at one time and the results will be known quickly. The results of genetic testing were defined as: pathogen mutation found or no pathogen mutation found. In other words, FH causing mutation found (FH+) or no FH causing mutation found (FH-).

**Informed consent**
DNA analysis was performed in patients with a high plasma LDL-C who gave their informed consent to diagnostic research in which patients have indicated to have no objection for the use of material for improvements in diagnostics.
**Statistical analysis**

IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. Categorical variables are given as number of patients and percentages. Continuous variables with equal distribution are represented as mean with standard deviation (SD). Continuous variables without equal distribution are given as median with interquartile range.

Comparisons of categorical variables between FH+ and FH- patients were carried out using the Chi-squared test, or the Fisher's exact test. Mean values of continuous variables were compared with the Student’s t-test for independent data. The relationship between variables was considered statistically significant with 2-tailed P-values <0.05.
Results

Patient characteristics
The study population consisted of 347 patients. However, 9 patients did not consent to genetic analysis or were too young. The remaining 338 patients were genetically analysed, either by the UMCG or the AMC. The UMCG analysed 125 patients, of which 23 patients had a FH causing mutation (FH+) and in 102 patients no pathogen mutation could be identified (FH-). The AMC investigated 213 patients, of which 104 FH+ and 108 FH- patients. The genetic results of one patient were unknown, which means that the genetic results of 337 patients were included. In total, there were 127 FH+ patients (37.7%) and 210 FH- patients (62.3%).

Patient characteristics of the entire study population are shown in Table 1. The characteristics of patients with and without a FH causing mutation are also included in this table. The study population consisted of 171 men and 176 women. The mean age was 47.6 years (range 5-88). In this table FH- and FH+ are compared.

Table 1. Baseline characteristics of hypercholesterolemia patients: total and divided by genetic tests into FH+ and FH- patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 347)</th>
<th>FH+ (N = 127)</th>
<th>FH- (N = 210)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.6 (17.7)</td>
<td>40.6 (19.2)</td>
<td>52.1 (15.0)</td>
<td>0.000</td>
</tr>
<tr>
<td>Male gender</td>
<td>171 (49.3)</td>
<td>58 (45.7)</td>
<td>110 (52.4)</td>
<td>0.232</td>
</tr>
<tr>
<td>Hypertension</td>
<td>113 (36.3)</td>
<td>28 (25.0)</td>
<td>82 (43.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking</td>
<td>76 (24.4)</td>
<td>23 (20.2)</td>
<td>53 (28.0)</td>
<td>0.126</td>
</tr>
<tr>
<td>Cardiovascular event*</td>
<td>95 (28.3)</td>
<td>22 (17.9)</td>
<td>68 (33.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8 (2.4)</td>
<td>1 (0.8)</td>
<td>7 (3.4)</td>
<td>0.267</td>
</tr>
<tr>
<td>MI</td>
<td>36 (10.7)</td>
<td>3 (2.4)</td>
<td>30 (14.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Angina</td>
<td>19 (5.7)</td>
<td>11 (8.9)</td>
<td>7 (3.4)</td>
<td>0.035</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>15 (4.5)</td>
<td>4 (3.3)</td>
<td>11 (5.4)</td>
<td>0.365</td>
</tr>
</tbody>
</table>

Lipid profile

First known

| TC (mmol/L) | 7.48 (1.95) | 7.79 (2.11) | 7.26 (1.80) | 0.032 |
| LDL-C (mmol/L) | 5.44 (1.81) | 5.78 (1.95) | 5.21 (1.69) | 0.032 |
| HDL-C (mmol/L)  | 1.24 (0.40) | 1.29 (0.38) | 1.19 (0.41) | 0.123 |
| Triglycerides (mmol/L) | 2.07 (1.82) | 1.31 (0.74) | 2.57 (2.11) | 0.000 |

Last known

| TC (mmol/L) | 5.44 (1.58) | 5.56 (1.59) | 5.36 (1.57) | 0.283 |
| LDL-C (mmol/L) | 3.51 (1.47) | 3.69 (1.53) | 3.40 (1.43) | 0.094 |
| HDL-C (mmol/L)  | 1.38 (0.47) | 1.44 (0.47) | 1.35 (0.47) | 0.104 |
| Triglycerides (mmol/L) | 1.67 (1.33) | 1.15 (0.73) | 2.00 (1.51) | 0.000 |

Statin use | 272 (83.4) | 103 (85.8) | 164 (83.7) | 0.607 |
| Statin intolerance | 72 (26.8) | 26 (26.5) | 44 (26.3) | 0.974 |

MI, myocardial infarction; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Of 1 patient were the results of the genetic tests unknown and 9 patients did not consent or were too young to be tested.

Values are expressed as number of cases and percentages, except for continuous variables that are expressed as mean and standard deviation (SD). P-value shows the (non)significance of group FH- compared to FH+.

*Cardiovascular events consist of cardiovascular death, nonfatal MI, cerebrovascular events (stroke, transient ischemic attack or intracranial hemorrhage), angina, heart failure, and peripheral arterial disease.
Table 1 shows that FH- patients were significantly older and more frequently had hypertension than FH+ patients. In the FH- group, 82 of 190 patients (43.2%) had hypertension, compared to 28 of 112 patients (25.0%) in the FH+ group (p=0.002). FH- patients were also at significant higher risk of cardiovascular events, in particular myocardial infarction. In the FH- group, 68 of 203 patients (33.5%) had a cardiovascular event, compared to 22 of 123 patients (17.9%) in the FH+ group (p=0.002). Myocardial infarction occurred more often in the FH- group, with 30 of 203 patients (14.8%), compared to 3 of 123 patients (2.4%) in the FH+ group (p=0.000). Although myocardial infarction was more frequent in FH- patients, angina was more common in FH+ patients (p=0.035). Angina occurred in 11 of 123 FH+ patients (8.9%), and in 7 of 203 FH- patients (3.4%). However, no significant difference in the number of smokers between FH+ and FH- patients was found (p=0.126).

First known lipid values of TC and LDL-C were higher in the FH+ population, while triglycerides were higher in the FH- population. In last known cholesterol values, no significant differences were present in TC and LDL-C, although triglycerides remained higher in FH- patients.

Table 2 shows the univariate and multivariate analysis of FH diagnosis on cardiovascular events. The results of the multivariate analysis were adjusted for age. FH- patients had a higher risk of cardiovascular events compared to FH+ patients, when adjusted for age [OR 1.99 (95% CI 0.53-7.44)]. Especially the risk of MI was high in the FH- group compared to the FH+ group [OR 2.78 (95% CI 0.48-16.03)]. However, the risk of angina in FH- patients was very low compared to FH+ patients.

Table 2. Univariate and multivariate analysis of the risk of cardiovascular events in patients with and without mutations. Multivariate analysis was adjusted for age.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Cardiovascular event*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH+ (22/123; 17.9%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>FH- (68/203; 33.5%)</td>
<td>2.31</td>
<td>1.34-3.99</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH+ (1/123; 0.8%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>FH- (7/203; 3.4%)</td>
<td>4.36</td>
<td>0.53-35.85</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH+ (3/123; 2.4%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>FH- (30/203; 14.8%)</td>
<td>6.94</td>
<td>2.07-23.25</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH+ (11/123; 8.9%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>FH- (7/203; 3.4%)</td>
<td>0.36</td>
<td>0.14-0.97</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH+ (4/123; 3.3%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>FH- (11/203; 5.4%)</td>
<td>1.70</td>
<td>0.53-5.48</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; OR, odds ratio; CI, confidence interval.
*Cardiovascular events consist of cardiovascular death, nonfatal MI, cerebrovascular events (stroke, transient ischemic attack or intracranial hemorrhage), angina, heart failure, and peripheral arterial disease.
Acquired causes of dyslipidemia
Table 3 shows the acquired causes of high LDL-C. The number of patients with obesity did not differ between FH+ and FH- patients (p=0.111). There was also no difference in diabetes between the FH+ and FH- group in this study (p=0.813). TSH levels were not different between FH+ and FH- (p=0.474). In FH+, 3 patients had TSH ≥4 mE/l, compared to 8 FH- patients.

Table 3. Prevalence of acquired causes of FH in mutation positive and negative patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 347)</th>
<th>FH+ (N = 127)</th>
<th>FH- (N = 210)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>52 (18.2)</td>
<td>19 (19.4)</td>
<td>33 (18.2)</td>
<td>0.813</td>
</tr>
<tr>
<td>Obesity</td>
<td>54 (18.4)</td>
<td>15 (13.9)</td>
<td>38 (21.5)</td>
<td>0.111</td>
</tr>
</tbody>
</table>

Renal function
First known
eGFR (ml/min) 92.36 (19.15) 96.91 (21.66) 90.21 (17.78) 0.057

Last known
eGFR (ml/min) 88.97 (18.41) 91.94 (17.70) 87.11 (18.59) 0.071
Micro albuminuria 23 (8.8) 6 (6.1) 17 (10.6) 0.218
Proteinuria 3 (1.1) 0 3 (1.9) 0.291

Thyroid function
TSH (mE/l) 1.48 [1.00-2.40] 1.40 [1.07-2.41] 1.60 [1.00-2.39] 0.394

eGFR, estimated glomerular filtration rate; TSH, thyroid stimulating hormone.
Of 1 patient were the results of the genetic tests unknown and 9 patients did not consent or were too young to be tested.
Values are expressed as n (%), means (SD), or medians [interquartile range].
P-value shows the (non)significance of group FH- compared to FH+.

Family history
More first-degree relatives in the FH- group had CVD, namely 127 of the 182 patients (69.8%), compared to 56 of the 104 patients (53.8%) in the FH+ group (Table 4). In the FH+ group more relatives had high cholesterol, both in first (p=0.000) and second-degree family members (p=0.000). In FH+ 101 of the 102 patients (99.0%) first-degree family members had high cholesterol, compared to 121 of the 140 patients (86.4%) in FH-. Second-degree family members with high cholesterol were found in 57 of the 58 patients (98.3%) in FH+ and in 29 of the 41 patients (70.7%) in FH-. The relative risks of having a first- or second-degree family member with high cholesterol in FH+ patients were respectively 1.15 [95% confidence interval (CI) 1.07-1.23] and 1.39 (95% CI 1.14-1.70) compared to FH- patients. The relative risks are also stated in the table below.

Table 4. Prevalence of CVD and high cholesterol levels in FH+ and FH- patients and their family members.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 347)</th>
<th>FH+ (N = 127)</th>
<th>FH- (N = 210)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relative with CVD</td>
<td>188 (63.9)</td>
<td>56 (53.8)</td>
<td>127 (69.8)</td>
<td>0.77 [0.63-0.94]</td>
<td>0.007</td>
</tr>
<tr>
<td>First degree relative with high cholesterol</td>
<td>228 (91.9)</td>
<td>101 (99.0)</td>
<td>121 (86.4)</td>
<td>1.15 (1.07-1.23)</td>
<td>0.000</td>
</tr>
<tr>
<td>Second degree relative with CVD</td>
<td>103 (67.8)</td>
<td>46 (69.7)</td>
<td>54 (66.7)</td>
<td>1.05 [0.84-1.31]</td>
<td>0.695</td>
</tr>
<tr>
<td>Second degree relative with high cholesterol</td>
<td>89 (87.3)</td>
<td>57 (98.3)</td>
<td>29 (70.7)</td>
<td>1.39 (1.14-1.70)</td>
<td>0.000</td>
</tr>
</tbody>
</table>
CVD, cardiovascular disease; RR, relative risk with 95% confidence interval (CI).
Of 1 patient were the results of the genetic tests unknown and 9 patients did not consent or were too young to be tested.
Values are expressed as number of cases and percentages.
P-value shows the (non)significance of group FH- compared to FH+.

Statin treatment
Table 5 shows the lipid concentrations in FH+ and FH- patients before and after treatment with statins. The number of patients in the table was lower than the original cohort for a number of reasons. A lot of patients in the study population did not receive statin treatment (e.g. patient was too young, resistance of a patient towards treatment, statin intolerance), started statin treatment after last cholesterol measurements, already were treated with a statin during both cholesterol measurements or statin use was unknown. Table 4 only includes patients who started using a statin after the first measurements and still used the statin during the final measurements.

Table 5. Lipid profile before and during treatment with statins.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 171)</th>
<th>FH+ (N = 57)</th>
<th>FH- (N = 112)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>7.94 (1.80)</td>
<td>8.44 (2.02)</td>
<td>7.63 (1.58)</td>
<td>0.010</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>5.95 (1.66)</td>
<td>6.43 (1.79)</td>
<td>5.68 (1.53)</td>
<td>0.024</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.16 (0.38)</td>
<td>1.23 (0.37)</td>
<td>1.13 (0.38)</td>
<td>0.192</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.20 (1.90)</td>
<td>1.31 (0.71)</td>
<td>2.68 (2.15)</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>During treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.96 (1.31)</td>
<td>5.16 (1.44)</td>
<td>4.86 (1.22)</td>
<td>0.156</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.05 (1.21)</td>
<td>3.33 (1.32)</td>
<td>2.90 (1.12)</td>
<td>0.031</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.33 (0.42)</td>
<td>1.39 (0.38)</td>
<td>1.31 (0.43)</td>
<td>0.262</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.71 (1.37)</td>
<td>1.06 (0.51)</td>
<td>2.07 (1.55)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
Of 1 patient were the results of the genetic tests unknown and 9 patients did not consent or were too young to be tested.
Values are expressed as mean and standard deviation (SD).
P-value shows the (non)significance of group FH- compared to FH+.

As seen in Table 5, TC and LDL-C values before treatment were significantly higher in the FH+ group: TC among FH+ patients: 8.44 ± 2.02 mmol/L versus 7.63 ± 1.58 mmol/L in FH-patients (p=0.010), LDL-C was also higher among FH+ patients: 6.43 ± 1.79 in FH+ patients versus 5.68 ± 1.53 mmol/L in FH- patients (p=0.024). Triglycerides were higher among the FH-group: 2.68 ± 2.15 mmol/L versus 1.31 ± 0.71 mmol/L in the FH+ group (p=0.000).

During treatment, TC levels did not differ significantly between FH- and FH+ (p=0.156). LDL-C levels were still higher in the FH+ group: 3.33 ± 1.32 mmol/L versus 2.90 ± 1.12 mmol/L in the FH- group (p=0.031). Many patients did not reach the target LDL value of 2.5 mmol/l or lower. After treatment, triglycerides were still higher in the FH- group: 2.07 ± 1.55 mmol/L versus 1.06 ± 0.51 mmol/L in the FH+ group (p=0.000).
Discussion

The present study shows that in the majority of patients living in the northern region of the Netherlands, despite a clinical phenotype of FH, no mutations for high LDL-cholesterol can be detected. No differences in acquired causes of FH between the two groups could be identified, pointing to a potential polygenetic cause in the FH- patients. Interestingly, FH+ patients and their family members have higher levels of LDL-C, but FH- patients and their first degree family members are more affected by cardiovascular events.

DNA analysis was performed in almost all patients. Only 9 patients did not give their consent or were too young to be tested. The genetic results of one patient were unknown, so 337 patients were tested in this study. A FH causing mutation was found in 127 patients (37.7%) and in the remaining 210 patients (62.3%) no FH causing mutation could be identified. These findings are in line with the study of Taylor et al. where no mutations were found in ~60% of FH patients (14). The majority of patients with a FH phenotype remains undiagnosed and are perhaps undertreated. Patients with a definite diagnosis of FH receive appropriate care and a diagnosis may increase the motivation of the patient to continue lifelong therapies. This indicates the need for other and more specific screening strategies (34).

When comparing the FH- patients to the FH+ patients, FH- patients were significantly older (52 versus 41 years). This could be explained by the fact that cascade screening was performed in relatives of FH+ patients and therefore younger individuals (i.e. children) were also genetically screened. These young children could then be quickly identified as carriers of a FH causing mutation and included in this study, which lowers the mean age in this group.

FH- patients were also more frequently hypertensive. The risk of myocardial infarction in FH-patients was six fold higher than in FH patients with mutations. However, after adjustment for age, the significant relation disappeared. Nevertheless, the risk of MI may be a problem in FH- patients, perhaps due to the fact that FH+ patients were stricter regulated and treated than FH- patients. Notably, angina was much more common in FH+ patients, even when adjusted for age. This may also be a result due to the more strict control of these patients, and diagnostic tests may be performed sooner in FH+ patients than in the others.

First known TC and LDL-C levels were high in FH- patients, but significantly higher in FH+ patients. Obviously, a FH causing mutation results in highly elevated TC and LDL-C concentrations, although the cause has been suggested to be polygenic rather than monogenic (35). First known and last known triglycerides were higher in the FH- group. This suggests other (unknown) genetic origins.

In FH- patients, more first-degree family members below the age of 60 years had CVD. This might be due to the fact that no FH causing mutation could be identified, and patients, including their families, were therefore automatically less strict controlled and treated when compared to the FH+ group and their relatives. Furthermore, no cascade screening was generally performed in contrast to the FH+ patients. The higher cardiovascular risk in these subjects strongly suggests that FH- patients and their relatives should be controlled and treated for their cardiovascular risk in the same way as FH+ patients. Furthermore, the identification of genetic causes for high LDL and cardiovascular events in FH- patients’ needs further research.
In FH+ patients, more first- and second-degree family members had high cholesterol levels. This is probably the result of cascade screening, where family members of FH+ patients with high cholesterol are identified.

During treatment, LDL-C concentrations in FH+ patients were still higher than in FH-patients. Remarkable is that both FH+ and FH- patients, on average, did not reach target LDL-C levels of <2.5 mmol/l with statins (18,49), which is in line with other studies (6,50).

**Acquired FH in FH- patients**
Hypothyroidism, type 2 DM, nephrotic syndrome, chronic renal failure and obesity were evaluated in this study. None of these potential acquired causes of high LCL-C significantly differed between FH- and FH+ patients. However, other causes such as cholestatic liver disease, excessive alcohol consumption and drugs were not evaluated.

**Limitations**
There are some limitations in this study regarding the applicability of the results. Since this is a retrospective study, not all variables could be retrieved from the patient files. For example, blood pressure, weight and height or laboratory results were not in all patients available.
Another limitation in this study is the fact that not all secondary causes of dyslipidemia were included in this study. These should be included to give a complete analysis of secondary causes. The most common conditions are diabetes mellitus and excessive alcohol intake, and we had no information about alcohol consumption.
The multivariate analysis in this study was adjusted for age, but not for hypertension. Since more FH- patients had hypertension, the non-significant differences in cardiovascular events between FH+ and FH- patients could be further reduced after adjustment for hypertension.

The first design of this study also included diagnostic sequencing of COMMD1 mutations in FH- and FH+ patients. These analyses are not yet performed and included in this study, due to a lack of time. The results of diagnostic sequencing and the effects on patients with a FH phenotype will be researched in follow-up studies. Further research need to be done, in order to fully understand the genetic pathway and influences on both FH+ and FH- patients.
Conclusions

In summary, this study shows in the cohort of patients with clinical suspicion of FH in the Groningen region, that no mutation can be found in 60% of the cases. Since no clear acquired factors of ADH could be identified, a polygenetic cause may be likely. Interestingly, FH-patients and their first-degree relatives had a high risk of cardiovascular events, in particular myocardial infarction. This implies that stringent control and treatment of secondary causes of dyslipidemia in FH-patients and their relatives is as important as in FH+ patients.
References


Phenotypic characterization of patients with familial hypercholesterolemia


(41) Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983 05/01;67(5):968-977.
Appendix

Appendix 1. MEDPED Criteria for FH

Appendix 2. Simon Broome Criteria for FH

Appendix 3. Dutch Lipid Clinic Network Criteria for FH
Appendix 1. MEDPED Criteria for FH
Medped criteria for diagnosing FH (22).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total and LDL-cholesterol (mmol/L) criteria for Diagnosing Probable Heterozygous Familial Hypercholesterolaemia (FH)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st degree relative with FH</td>
</tr>
<tr>
<td>&lt;20</td>
<td>7.5 (4.0)</td>
</tr>
<tr>
<td>20–29</td>
<td>7.2 (4.9)</td>
</tr>
<tr>
<td>30–39</td>
<td>7.8 (5.6)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>7.5 (5.3)</td>
</tr>
</tbody>
</table>
| TC = total cholesterol.

Appendix 2. Simon Broome Criteria for FH
Simon Broome criteria for diagnosing FH (23).

**Definite FH**
Raised cholesterol:
- In children (<16 years): total cholesterol > 6.7 mmol/L OR LDL-C > 4.0 mmol/L
- In adults (≥16 years): total cholesterol > 7.5 mmol/L OR LDL-C > 4.9 mmol/L
- AND
  - Tendon xanthomata in the patient or in a first or second degree relative
  - OR
  - DNA-based evidence of a LDL-receptor, familial defective apo B-100 or PCSK9 mutation

**Possible FH**
Raised cholesterol:
- In children (<16 years): total cholesterol > 6.7 mmol/L OR LDL-C > 4.0 mmol/L
- In adults (≥16 years): total cholesterol > 7.5 mmol/L OR LDL-C > 4.9 mmol/L
- AND one of the following:
  - Family history of premature myocardial infarction
  - MI at <50 years in second degree relatives.
  - OR
  - Family history of raised cholesterol
- In adult (≥16 years), first or second degree relatives: total cholesterol > 7.5 mmol/L
- In child (<16 years), first degree relatives: total cholesterol > 6.7 mmol/L
Appendix 3. Dutch Lipid Clinic Network Criteria for FH

Dutch Lipid Clinic Network Criteria for making a diagnosis of FH in adults (24).

<table>
<thead>
<tr>
<th>Diagnostic scoring table for FH (constructed by the Dutch Lipid Clinic Network)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history</strong></td>
</tr>
<tr>
<td>a First degree relative known with premature (men &lt; 55 yrs, women &lt; 60 yrs) coronary and vascular disease: 1</td>
</tr>
<tr>
<td>b First degree relative known with LDL-cholesterol &gt; 95(^{th}) percentile. and/or 2</td>
</tr>
<tr>
<td>and/or First degree relative with tendon xanthomata and/or arcus cornealis. 2</td>
</tr>
<tr>
<td>a Children below 18 yrs. with LDL-cholesterol &gt; 95(^{th}) percentile. 2</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
</tr>
<tr>
<td>a Patient has premature (men &lt; 55 yrs, women &lt; 60 yrs) CAD 2</td>
</tr>
<tr>
<td>b Patient has premature (men &lt; 55 yrs, women &lt; 60 yrs) cerebral or peripheral vascular disease. 1</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
</tr>
<tr>
<td>a Tendon xanthomata                                         6</td>
</tr>
<tr>
<td>b Arcus cornealis below the age of 45 yrs.                  4</td>
</tr>
<tr>
<td><strong>Laboratory analysis</strong></td>
</tr>
<tr>
<td>a LDL-cholesterol &gt; 8.5 mg/dl &gt; 330 mmol/l                  8</td>
</tr>
<tr>
<td>b LDL-cholesterol 6.5 - 8.4 mg/dl 250-329 mmol/l            5</td>
</tr>
<tr>
<td>c LDL-cholesterol 5.0 - 6.4 mg/dl 190-249 mmol/l            3</td>
</tr>
<tr>
<td>d LDL-cholesterol 4.0 - 4.9 mg/dl 155-189 mmol/l (HDL-cholesterol and triglycerides are normal) 1</td>
</tr>
<tr>
<td><strong>DNA-analysis</strong></td>
</tr>
<tr>
<td>a Functional mutation low-density lipoprotein receptor gene present 8</td>
</tr>
<tr>
<td><strong>Diagnosis of FH is:</strong></td>
</tr>
<tr>
<td>certain when &gt; 8 points</td>
</tr>
<tr>
<td>probable when 6-8 points</td>
</tr>
<tr>
<td>possible when 3-5 points</td>
</tr>
</tbody>
</table>
Abstract in Dutch

Achtergrond
Familiaire hypercholesterolemie (FH) is een autosomaal dominant overervende aandoening. Deze aandoening is geassocieerd met een sterk verhoogd risico op hart- en vaatziekten en overlijden op relatief jonge leeftijd. De aandoening wordt gekenmerkt door hoge concentraties totaal cholesterol (TC) en low-density lipoprotein cholesterol (LDL-C). FH is het gevolg van mutaties in de genen die coderen voor de low-density lipoproteïne-receptor (LDLR), in bepaalde delen van het apolipoproteïne B (APOB), en proprotein convertase subtilisin/kexin type 9 (PCSK9). Echter in het overgrote deel van de patiënten met een klinisch FH fenotype kan met de gebruikelijke, hedendaagse technieken geen pathogene mutatie worden aangetoond. In deze studie werden mogelijke verworven oorzaken van FH onderzocht in FH mutatie negatieve patiënten en werd het cardiovasculaire risico geëvalueerd bij patiënten en familieleden met en zonder mutaties.

Methode
Deze retrospectieve studie omvatte 347 patiënten met een fenotype van FH. Alle patiënten waren bekend in het Universitair Medisch Centrum Groningen (UMCG). Genetisch onderzoek werd, na toestemming uitgevoerd in 337 patiënten. Lipidenwaarden, cardiovasculaire gebeurtenissen, secundaire oorzaken van dyslipidemie, familiare voorgeschiedenis van hart- en vaatziekten en hypercholesterolemie, en de resultaten van de genetische tests werden verkregen met behulp van de digitale patiënten database van het ziekenhuis. Deze gegevens werden vergeleken tussen patiënten met een bekende FH veroorzakende mutatie (FH+) en patiënten bij wie geen pathogene mutatie kon worden aangetoond (FH-).

Resultaten
In totaal waren er 127 FH+ patiënten (37.7%) en 210 FH- patiënten (62.3%), terwijl bij 10 patiënten de genetische testresultaten niet bekend waren. De gemiddelde leeftijd was 47.6 jaar. FH- patiënten waren significant ouder en hadden vaker hypertensie. De prevalentie van cardiovasculaire gebeurtenissen, in het bijzonder myocardinfarct was hoger in de FH-patiëntengroep. Terwijl meer familieleden van FH+ patiënten ook een hoog cholesterol hadden, waren er meer hart- en vaatziekten onder de eerstegraads familieleden in de FH-groep. Geen van de secundaire oorzaken verschilde significant tussen FH- en FH+ patiënten. Veel FH+ en FH- patiënten hebben, gemiddeld, niet de doel LDL-C van <2.5 mmol/l kunnen behalen met statines.

Conclusies
In 60% van de patiënten met een klinische verdenking op FH kon geen mutatie worden gevonden. Er konden geen duidelijke verworven oorzaken van FH worden geïdentificeerd, wat mogelijke wijst op een poly genetische oorzaak van hoge cholesterol concentraties. Interessant is dat FH- patiënten en hun eerstegraads familieleden een hoger risico hebben op het doormaken van cardiovasculaire aandoeningen, in het bijzonder myocardinfarct. Strikte controle en behandeling van secundaire oorzaken van dyslipidemie in FH- patiënten is net zo belangrijk als bij FH+ patiënten.