Management of Patients with Familial Hypercholesterolemia

cure and care

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behandeling en begeleiding

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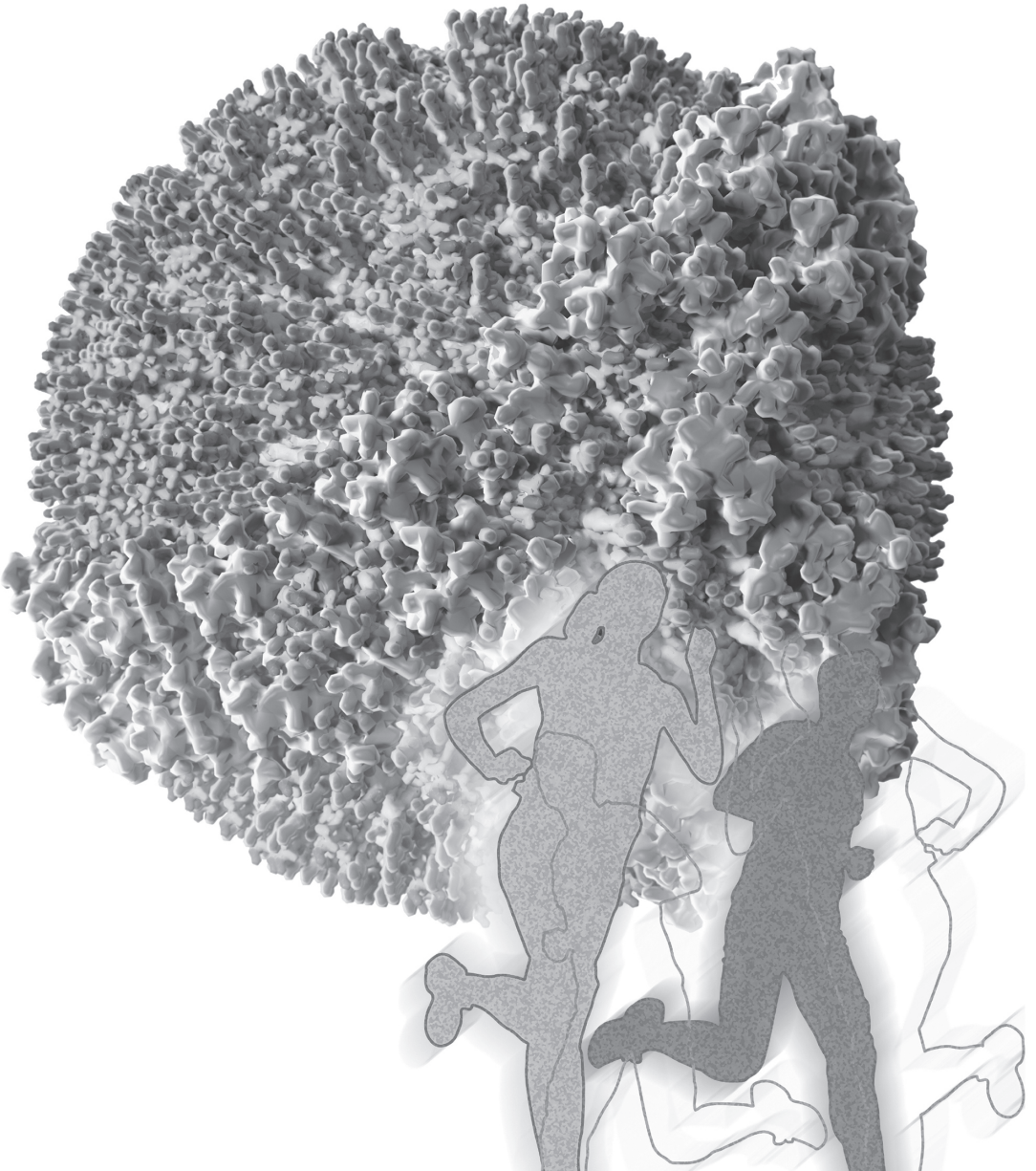

Chapter 1
Introduction

Management of Patients with familial hypercholesterolemia:

cure and care

Cardiovascular disease and risk factors

Cardiovascular disease (CVD) is the leading cause of death in middle aged men and women globally [1]. The process of atherosclerosis starts already in childhood and during the life course various risk factors contribute to the further development of atherosclerosis, eventually leading to CVD later in life [2]. Therefore CVD is an outcome of an interplay between long-standing risk factors. Traditional risk factors are smoking, physical inactivity and unhealthy diet leading to metabolic changes such as overweight or obesity, hypertension, diabetes mellitus and hypercholesterolemia [3]. Hypercholesterolemia has been identified as one of the major risk factors for developing and progression of atherosclerosis.
This thesis focuses on diagnosis, risk prediction and management of familial hypercholesterolemia (FH), the most common monogenetic disorder causing hypercholesterolemia.

Introduction to familial hypercholesterolemia

FH is an autosomal dominant disorder of the lipid metabolism with an estimated prevalence of 1:244 in the Netherlands [4]. FH is caused by loss of function mutations in genes encoding for the low-density lipoprotein-receptor (LDLR), apolipoprotein B (APOB) and gain of function mutations in the PCSK9 gene. The diagnosis FH can be made genetically by DNA analysis or clinically by using the Dutch Lipid Clinic Network Criteria (table) [5].
FH is associated with a severe risk of premature CVD [6, 7]. Untreated, the risk of CVD in men and women with FH is 50% before the age of 50 years and 30% before the age of 60 years respectively [8].
In the Netherlands, a nationwide population cascade screening program in families with a pathogenic variant causing FH has been carried out between 2001-2013. Of the estimated 70.000 people with FH in our country, almost 30.000 have been diagnosed [9]. The majority of these FH patients were identified through cascade screening, based on one index patient of a family.

Table: Dutch Lipid Network Criteria for FH [10]

Family history	**points**
First-degree relative with premature coronary and/or vascular disease (men ≤55 years, women ≤60 years), OR first-degree relative with known LDL-cholesterol ≥95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR Children aged ≤18 years with known LDL-cholesterol ≥95th percentile for age and sex	2
Clinical history	
Patient with premature coronary artery disease (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical examination	
Tendon xanthomas	6
Arcus cornealis at age ≤45 years	4
LDL-Cholesterol levels mmol/L (mg/dL)	
LDL-C ≥8.5 (330)	8
LDL-C 6.5 - 8.4 (250 - 329)	5
LDL-C 5.0 - 6.4 (190 - 249)	3
LDL-C 4.0 - 4.9 (155 - 189)	1
DNA Analysis	
Functional mutation LDLR, APOB and PCSK9	8

Diagnosis FH
Definite FH: >8 points.
Probable FH: 6-8 points.
Possible FH: 3-5 points.

Management of familial hypercholesterolemia

Management of patients with FH consists of a combination of lifestyle modification and medical treatment.

Treatment by lifestyle modification

Classical vascular risk factors such as smoking, overweight, inactivity, hypertension and diabetes mellitus are similar to non-FH individuals associated with an increased CVD risk in FH patients [11, 12]. Therefore guidelines highly recommend lifestyle modification [13]. Although no trials have been performed to study the effect of lifestyle intervention specifically in FH patients, there is no reason to assume that the results of lifestyle intervention are different for people with or without FH. Lifestyle modification; such as smoking cessation, weight reduction, sufficient physical exercise and a healthy diet can play an important role in the delay of progression of atherosclerosis in patients with an increased CVD risk [14]. However it is well established that the success of long-term lifestyle modification is limited. Therefore, the most successful approach of CVD risk prevention is to promote a healthy lifestyle from early age onwards ideally starting in children with FH. But even with a healthy lifestyle, the cardiovascular risk of FH is still elevated compared to non-FH subjects [15].

Current medical treatment

The cornerstone of medical treatment is a timely start with lipid-lowering therapy (LLT). HMG-coenzyme A inhibitors also known as statins were first introduced in the 1976 and received wide publicity since the Scandinavian Simvastatin Survival Study Group trial showed that statins are associated with LDL-C reduction leading to decreased CVD events [16, 17]. Statin treatment can be considered as causal therapy for FH patients. During previous decades more and more potent statins were developed with increased LDL-C lowering potential. Numerous randomized clinical trials showed that statins lower CVD risk and also demonstrated that CVD risk was inversely related to LDL-C levels. The efficacy of statin treatment in FH patients without CVD is much higher than observed in most large primary prevention trials; 76% versus approximately 37% CVD risk reduction, respectively [18]. In FH patients using statins, the addition of the Niemann-Pick C1-like 1 receptor antagonist ezetimibe led to LDL-C reduction but not to improvement of subclinical atherosclerosis represented by intima media thickness [19]. Later on the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that patients with CVD who were randomized to ezetimibe in addition to statins, developed less "hard-end-

points" namely cardiovascular events compared to patients who used statin monotherapy [20]. Thereby proving that LDL-C reduction is associated with decrease in cardiovascular events, independent of how this is achieved. However even despite optimal current LLT some FH patients still develop CVD.

New lipid lowering therapy

Recently Proprotein convertase subtilisin / Kexin (PCSK9) inhibitors, a new class of LLT have been developed. Randomized controlled trials, demonstrated that these monoclonal antibodies can further lower LDL-C levels up to 60% [21, 22]. This new drug has potentially advantages being highly effective and has a favourable safety profile. However, it is important to ensure that data from clinical trials apply to real-life settings as well, especially when it concerns long term safety. Therefore "real life data" are needed to improve the applicability of the trial evidence to daily practice.

Adherence of medication

Adherence is defined as 'the extent to which patients follow the recommendations by their healthcare professional' [23]. Non-adherence to prescribed drug regimens is a pervasive medical problem. In general, adherence rates are low in patients with chronic diseases. Non-adherence or partial adherence is a problem in patients with CVD, as these patients have significant higher risk of cardiovascular events compared to patients who are fully adherent [24]. Many different factors such as primary prevention, side effects and low level of education have been associated with poor adherence to medication. In patients with FH adherence is a continuous challenge as they have to adhere to life-long medication without short-term benefit. Only a minority of FH patients treated with lipid-lowering medication achieve their LDL-C treatment goal [25], however it is not known whether this poor result is attributable to poor adherence. Moreover, it is unknown which factors are associated with adherence in the FH population. Potentially there is much to be gained by improving adherence. A number of possibilities can contribute to adherence such as motivational interviewing, follow-up by the Medication Electronic Monitoring System (MEMS) and strategies for enhancing self-efficacy [26-28]. However, it all starts with recognizing non-adherence as a problem.

The role of the nurse practitioner

FH patients have a chronic disorder, they are advised to use lifelong medication and to take lifestyle changes into account. Maintaining a healthy lifestyle con-

sisting of non-smoking, a healthy diet, sufficient physical exercise in combination with an adequate medication intake, are considered essential components of self-management [29]. Improving self-management by optimizing risk factors modification contribute to successful CVD prevention [30, 31]. Nurse practitioners (NP) are educated in providing tools for promotion of self-management and self-efficacy as well as medical treatment combining both care and cure. In addition to providing education about FH, cardiovascular risk factors and counselling in health behaviour, a NP can prescribe and modify medication but also offer patient education for example how to use new medication such as PCSK9 inhibitors. Therefore the integrated approach of the NP can have an important place in the treatment of FH patients.

Special populations in clinical management of familial hypercholesterolemia

Children with familial hypercholesterolemia

In children with FH, the process of atherosclerosis and elevated LDL-C levels starts early in childhood. Potentially individuals with FH can have a normal life expectancy if treatment starts early. Recommendations to commence treatment with low doses of statin and a healthy lifestyle at young age are recommended in the European consensus for management of children with FH [32]. Therefore identification of these young subjects through active cascade screening is a necessity.

Women with familial hypercholesterolemia

Recently more awareness and attention has been paid to gender-specific medicine. Traditionally men were the standard and research including drug trials were confined to men. Little is known about gender-differences in the management of FH patients. In general statins have a similar efficacy in men and women, however it is unclear whether women experience more statin associated side effects [33, 34]. Therefore it is essential to investigate potential gender differences in management of FH patients and the factors contributing to the treatment among women and men.

Aims and outline of thesis

This thesis addresses gaps in knowledge in diagnosis and management of patients with FH. The aim of these studies is not only to describe the current status but also provide clinical tools how diagnosis, risk prediction and management can be further improved for these patients in clinical practice.

The thesis consists of studies dedicated to the diagnosis and risk prediction of patients with FH (chapter 2,3,4) and the second part (chapter 5,6,7) comprises studies on the management of patients with FH.

In **chapter 2** we investigate issues concerning dyslipidemia testing in general such as why should lipids be tested, in whom, and when should they be tested.

In **chapter 3** we investigate the success of our cascade screening program by assessing whether children with FH have been identified through cascade screening or due to CVD in the FH parent.

In **chapter 4** we assess the residual risk of cardiovascular events in heterozygous FH patients who use long-term lipid lowering therapy.

Chapter 5 presents a prediction model for identification of FH patients, who are non-adherent to statin therapy.

In **chapter 6** we study the differences in the management of FH patients between men and women.

Chapter 7 describes the first experiences with Proprotein convertase subtilisin/Kexin 9 (PCSK9) inhibition in patients with FH outside clinical trials.

This is followed by the general discussion and summary.

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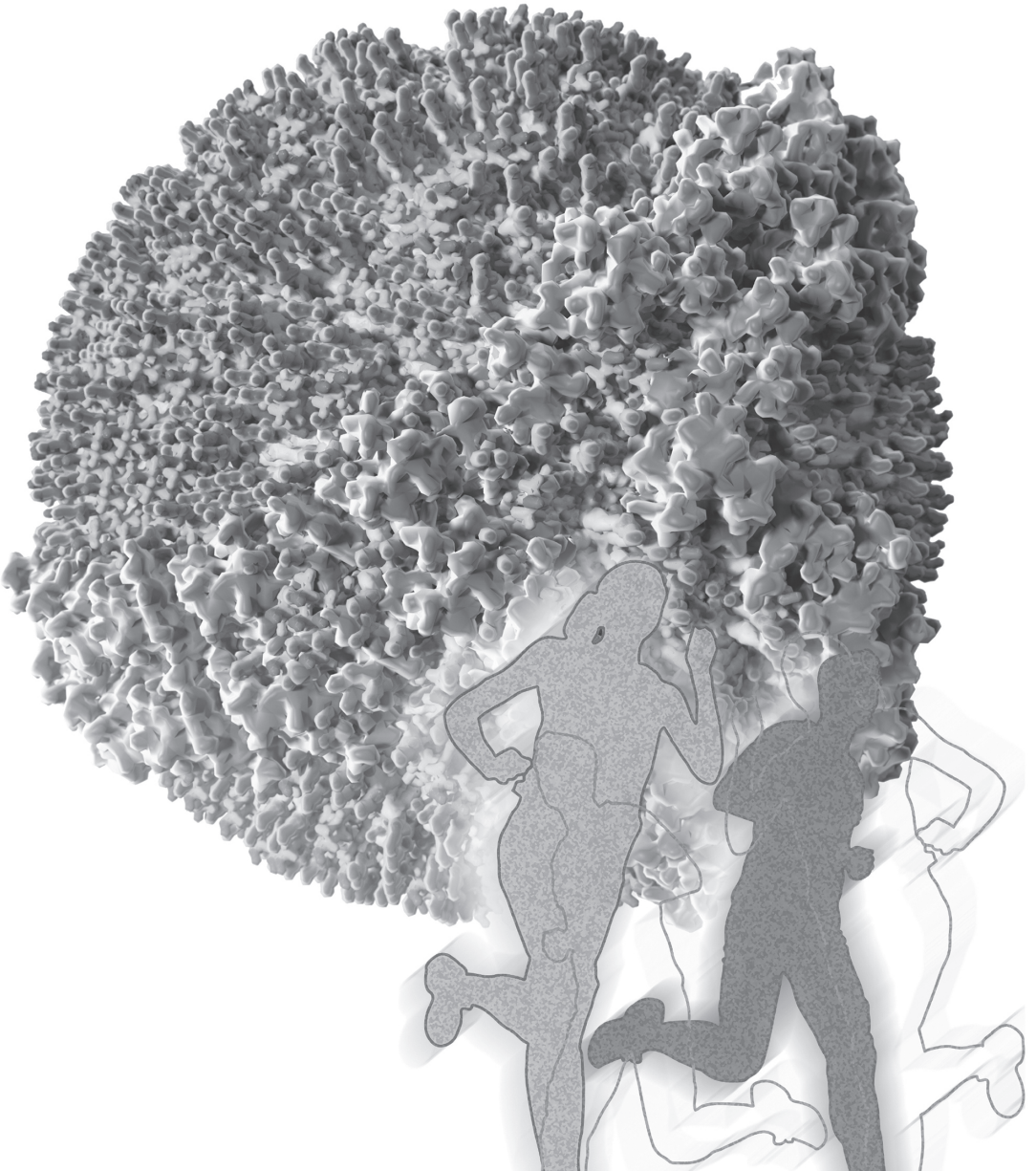
Part 1

Diagnosis and risk prediction of patients with familial hypercholesterolemia



Chapter 2

Dyslipidemia testing: Why, for whom and when

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Abstract

Dyslipidemia is a major risk factor for cardiovascular disease. This review addresses why, who and when to test for dyslipidemia. The essence why to test lipids is that those individuals recognized to potentially benefit from cardiovascular risk prevention, have a complete cardiovascular risk assessment. Who and when to test lipids differs among the major European, English and American guidelines regarding the recommended age and approach. It is important to note that the threshold and the frequency in whom to perform risk assessment is not established. Most important in decisions concerning lipid testing is communication and to involve individual circumstances.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in middle-aged and older adults globally [1]. CVD can be considered to be the outcome of an interplay between long-standing risk factors [2]. One of the most indisputably established risk factors for developing and progression of atherosclerosis is dyslipidemia [3, 4]. Dyslipidemia covers a broad spectrum of lipid abnormalities, including elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride levels and low high-density lipoprotein cholesterol (HDL-C) levels which have been associated with increased risk of CVD risk. For patients with CVD, it is generally agreed upon by all guidelines that lipid testing -at least at baseline- is mandatory. However, in people without CVD this is not as well-defined.

This review will focus on lipid testing in primary cardiovascular prevention and will discuss the following questions concerning dyslipidemia testing: why should we test lipids? In whom should we test lipids and when should we test them?

Why test lipids?

The starting point of lipid testing should be the decision to perform a cardiovascular risk assessment of which testing lipids is one component. It is essential to first determine whether a certain individual is likely to benefit from CVD risk intervention. Factors which affect the judgement whether or not assessing cardiovascular risk is appropriate or not are life expectancy, time to benefit and functional status. The results of cardiovascular risk assessment -including lipid levels- can be used to identify those who are likely to benefit from specific interventions and may support the dialogue between a health care professional and the patient if and how to modify cardiovascular risk. It is important to emphasize that the main goal to test lipids should be broader than to identify those who qualify for lipid-lowering therapy but also include lifestyle modification [5-8]. In the case treatment is needed, safe and effective drug treatment is available. Especially statin therapy has been shown to very effectively lower CVD in both primary and secondary prevention [9-11].

Therefore, the core why to test lipids is that those individuals recognized to potentially benefit from cardiovascular risk prevention, have a complete cardiovascular risk assessment.

Who to test?

The opinion for who prevention of CVD is efficacious can be captured by two main approaches: the population-based strategy and the high risk strategy. Both

lines are meaningful and complement each other. The population-based strategy aims to decrease the overall risk profile in the general population. This can be accomplished by preventive measures on a large scale for example if butter would be replaced by margarine in the supermarket. On population level this could lead to lower cholesterol levels and subsequent lower CVD. However, for the individual the gain will be small, hence this is known as the prevention paradox [12].

The high risk approach focuses on identifying individuals at elevated risk of cardiovascular disease. The decision to screen for lipid levels is based on the probability that the results might lead to an overall risk of CVD high enough for intervention such as lipid-lowering therapy. This approach aimed to target the risk of the individual, is considered a more cost-effective use of limited resources in comparison with mass screening [12]. Targeted cardiovascular screening can identify up to 84% of high-risk individuals, which can be considered a good yield [13].

Who should we test according the guidelines?

Among the guidelines no uniformity exists in the recommendations in whom to test lipids. We summarized and compared three high risk strategy guidelines for prevention of CVD in primary cardiovascular prevention setting (table 1). The objective of all these guidelines is to provide recommendations how to prevent (recurrent) CVD by estimating the probability of the 10-years or life-time risk of a first cardiovascular event in individuals. The high risk strategy guidelines use risk estimation systems based on different longitudinal cohort studies of several countries. Finally, we describe the American Heart Association (AHA) 2020 impact goals, a population-based strategy.

The latest version of the Systematic Coronary Risk Evaluation (SCORE) is used in the ESC/EAS guideline 2012. Separate charts are used depending on sex, smoking status, age groups, hypertension and total cholesterol/HDL-C ratio. CVD screening including lipid testing is recommended in all men of ≥40 years, and women ≥50 years or if postmenopausal, particularly in the presence of other risk factors based on the SCORE estimation. Special high risk groups such as those with chronic kidney disease (CKD), familial hypercholesterolemia (FH) and type 1 or type 2 diabetes mellitus (DM) with micro-albuminuria, qualify for lipid screening irrespective of age [5].

The Joint British Societies (JBS3) recommendations of CVD risk assessment and modification of blood lipids are closely linked to National Institute for Health and Care Excellence (NICE) [6, 8]. They published the most recent guideline in 2014. Their QRISK2 risk calculator is based on risk factors such as age, sex, cho-

Table 1. Recommendation of lipid testing regarding primary prevention according to cardiovascular risk prevention guidelines.

Lipid testing	Why	Who	When
Risk based guidelines ESC/EAS [5]	• Preventing CVD • Lowering CVD risk	Men ≥40 years, women≥50 years or postmenopausal, particularly in the presence of other risk factors Early lipid screening irrespective of age for; • Patients with CKD • Chronic inflammatory disease • Family history of FH and/or CVD • Severe hypertension • Patients with DM and organ damage • Smoking and/or BMI ≥30 kg/m^2	During a consultation • Before starting lipid lowering therapy; 2 measurements should be made 1-12 weeks interval • 8 (±4) weeks after starting drug treatment • Once a year when a patient has reached target or optimal cholesterol • More frequent when there is an adherence problem
NICE and JBS3 [6,8]	• Preventing CVD • Lowering CVD risk	All adults aged ≥40 years Special groups; • Adults of any age with a family history of premature CVD (men ≤55 years/women ≤60 years). • All individuals with a first degree relative with FH. • Adults with DM, RA, CKD and hypertension.	Every 5 years • Following lifestyle modification • Once a year when a patient has reached target or optimal cholesterol
ACC/AHA [7]	• Preventing CVD • Lowering CVD risk	• All adults aged ≥20 years Special groups: • LDL-C ≥ 90 mg/dl • DM aged 40-75 years and LDL 70-189 mg/dl • Without DM aged 40-75 years with 10-year ASCVD risk ≥7.5% • Children and first degree relatives of patients ≥190 mg/dl screening for FH	Every 5 years in individuals 40-75 years old without CVD or DM and with a LDL-C 70-189 mg/dl • Before starting lipid lowering therapy; 2 measurements should be made 1 -12 weeks interval • 4-12 weeks after starting drug treatment • Every 3-12 months as clinically indicated • Annually in FH patients

ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; NICE, National Institute for Health and Care Excellence, JBS3, Joint British Societies; ACC/AHA, American College of Cardiology/American Heart Association; CVD, cardiovascular disease; FH, familial hypercholesterolemia; DM, diabetes mellitus; RA, rheumatoid arthritis; CKD, chronic kidney disease; LDL-C, low density lipoprotein-cholesterol; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease.

lesterol/HDL ratio, blood pressure and/or use antihypertensive medication, DM, smoking status, ethnicity, region of United Kingdom, family history of coronary heart disease (CHD) before age 60, deprivation, body mass index (BMI), rheumatoid arthritis (RA), CKD, and atrial fibrillation. These guidelines do not only focus on identifying and treating individuals with >10% CVD risk within 10 year but also incorporate lifetime risk assessment aiming at individuals who will have a potential benefit of lowering risk factors. In the United Kingdom adults 40 to 74 years are invited for the National Health Service (NHS) Health Check programme by general practices and other health care providers to have their lipids tested. An exception exists for those with (suspected) FH for whom lipid testing is advised at the age of 10 years or as soon as possible thereafter [14].

In 2013 the American College of Cardiology (ACC)/AHA guideline developed

a new atherosclerotic cardiovascular disease (ASCVD) risk estimator, based on age, sex, race, blood pressure and/or use antihypertensive medication, DM, smoking status and cholesterol/HDL ratio to estimate the 10-year CVD risk. Contrary to the previous guidelines, the ACC/AHA guideline recommends lipids to be measured as early as 20 years of age in all individuals, with special emphasis on those whom most likely benefit from statins such as those aged 40-75 years with either DM or with a 10 years risk ≥7.5% and a LDL-C 70-189 mg/dL. Individuals with a LDL-C ≥190 mg/dl and their first degree relatives are advised to have their lipids tested as part of FH screening without a lower threshold of age [7, 15].

In the United States the AHA has initiated a shift from secondary and primary prevention towards primordial prevention by a comprehensive public health strategy to prevent cardiovascular diseases emphasized by lifestyle modification and supported by cost-savings data [16, 17]. The 2020 impact goals developed by the AHA deliberately chooses to emphasize the development of healthy lifestyle beginning in childhood and adolescence, continuing throughout life course. The aim is to lower risk and burden of CVD by promoting cardiovascular health. To measure cardiovascular health the AHA has developed a cardiovascular health score based on three health factors: blood pressure, fasting glucose and total cholesterol and four health behaviors; smoking status, physical activity, healthy diet and BMI. Lipid testing throughout the life course is advised for everybody including children [18].

In conclusion, the recommendation in whom to test lipids in primary prevention setting, differs among the aforementioned high-risk guidelines regarding age and particular population whereas the population-based strategy advocates lipid testing for all.

When to screen

How often CVD screening, including lipid testing, should be repeated in individuals without CVD, is not described in every guideline. The ESC/EAS guidelines designate the general practitioner as central health care provider to initiate and coordinate lipid testing in the process of CVD prevention and does not specify an interval when retesting lipids is advised unless lipid-lowering treatment is initiated.

The NICE guideline suggests to offer people the opportunity to recalculate their CVD risk after lifestyle modification. How active or intensive the approach for risk assessment will be, always depends on the health care provider and the motivation of the patient. A confident patient-clinician relation and awareness

of risk behaviour is essential to achieve lifestyle changes [19].
According the ACC/AHA guidelines the estimated 10-year ASCVD can be recalculated every 5 years in individuals 40-75 years without ASCVD or DM and with LDL-C 70-189 mg/dL. Longer intervals are recommended for those without an increased risk and normal lipid levels [7, 15]. Hence, recommendations regarding the frequency of lipid testing vary among guidelines.

Conclusion

Before lipid testing every clinician should ask the question: What do the results mean to my patient? A systematic risk stratification to identify those at the highest risk is required. European, British and American guidelines are all based on a risk calculator but differ in their recommendations concerning lipid testing. What they have in common is that they advocate an integrated approach with the engagement of the patient as a partner in CVD prevention.
Nonetheless, despite all guidelines, in the end decisions concerning lipid testing are about communication with the patient involving individual circumstances including why, who and when.

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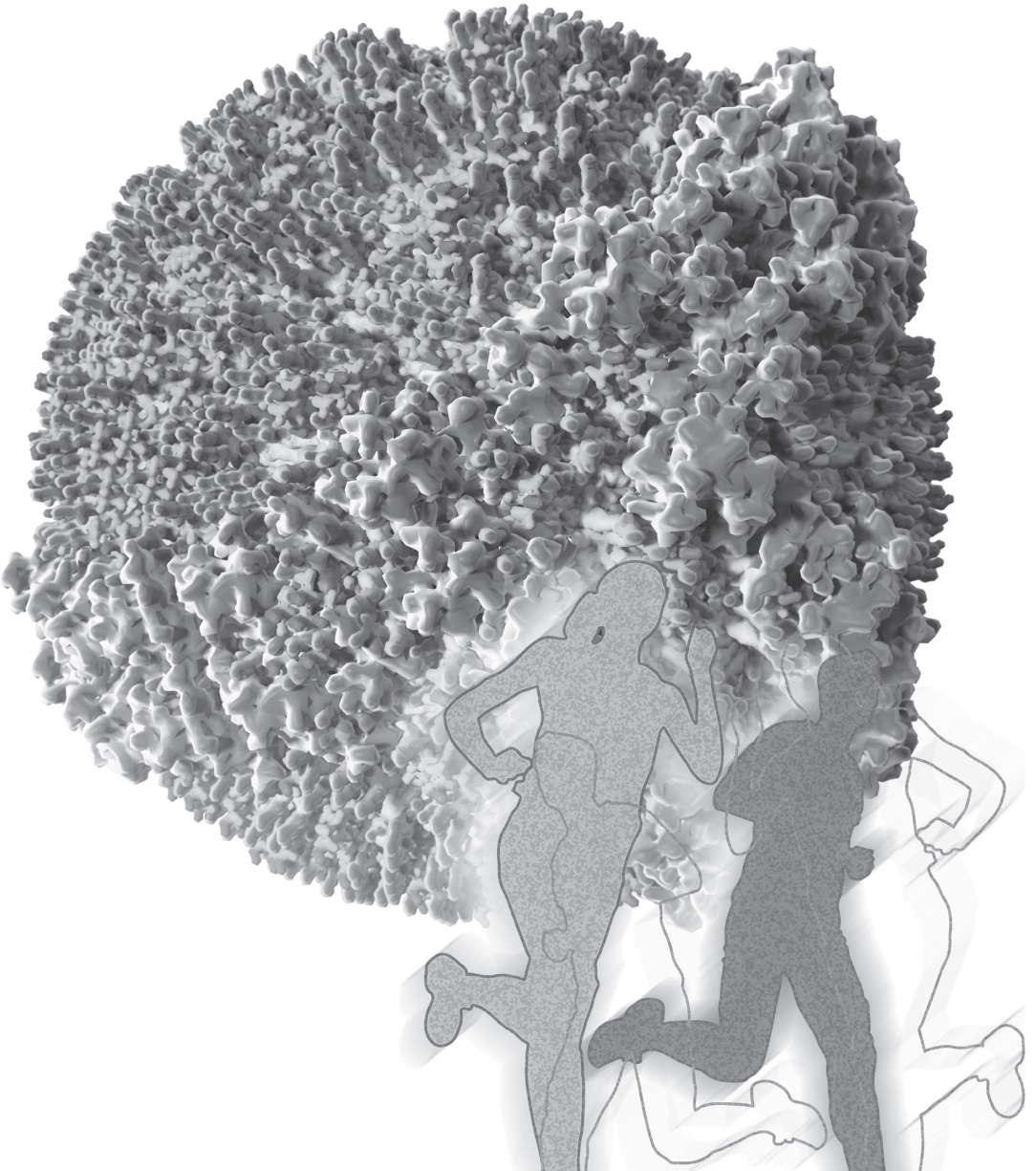

Chapter 3

Cascade screening of familial hypercholesterolemia must go on

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Abstract

Purpose

This study assesses the success of the recently terminated Dutch nationwide cascade screening by examining whether children with familial hypercholesterolemia (FH) were identified through family screening or due to cardiovascular (CVD) events in the FH parent.

Methods

We collected clinical information of all children (0-18 years) with FH with a pathogenic variant at our outpatient lipid clinic between 1992 and 2014 and their FH parents and FH grandparents.

Results

We analysed 292 FH children from 205 parents with FH. A history of premature CVD was present in 20% of the parents (29% of the fathers, 9% of the mothers) and 49% of the FH grandparents.

Conclusion

The fact that CVD is still a presenting event of FH in especially fathers shows that nationwide screening might have been terminated too early. Therefore we recommend to proceed the cascade screening.

Introduction

Familial hypercholesterolemia (FH) is a disorder of lipid metabolism associated with a severe risk of cardiovascular disease (CVD) [1, 2]. Effective CVD prevention is available, consisting of lifestyle changes and lifelong statin treatment [3, 4]. Recent data showed that FH is more prevalent in the Netherlands than previously assumed: these data suggest that the prevalence might be as high as 1:244 [5]. In The Netherlands a well-known nationwide cascade screening in families with a pathogenic variant causing FH has been carried out over the last 15 years. This program, supported by the Dutch Ministry of Public Health, Welfare and Sport, involved genetic fieldworkers who visited relatives at home, and collected medical information and blood samples. Due to end of funding, this national cascade screening program has terminated at the end of 2013. At that moment >28.000 people with FH were identified, 42% of the expected number of FH patients in The Netherlands [6]. The aim of the program is that FH patients are identified through cascade family screening rather than as a consequence of CVD bringing them into clinical attention. A method to assess the success of our cascade screening program is to study whether children with FH have been identified through cascade screening or due to CVD in the parents. The aim of this study was to identify how many of the children treated at our clinic were referred because of a parent with CVD.

Patients and methods

Participants

All consecutive children with FH who visited the outpatient lipid clinics of the Erasmus MC or Sophia Children Hospital The Netherlands for the first time with an age ≤18 years, between April 1993 and November 2014 were considered eligible for inclusion in this study. The diagnosis FH was based on identification of a FH pathogenic variant in the LDL-receptor (LDLR) gene or the Apolipoprotein B (APOB) gene. The variants in patients were reviewed by a specialist of the laboratory that identified and characterized these variants (dr. ir. J. Defesche). All variants presented in this study were pathogenic variants, either because they have been published as pathogenic by in vitro activity assays or by co-segregation in families. Children diagnosed with FH based on clinical grounds were excluded.

The Medical Ethical Review Committee of the Erasmus MC, The Netherlands, considered the protocol non-Medical Research Involving Human Subjects Act (WMO) therefore review of the protocol was waved.

Study design
FH patients are treated by the Cardiovascular Genetics (CVG) team consisting of a lipidologist, a nurse practitioner and a research nurse specialized in collecting pedigree data. Parents are advised to bring their children from the age of 10 years for follow-up. Children and parents with FH receive regular tailored education about their disease, lifestyle advices, benefits of using statins and the effect of treatment on lipid profiles.
Clinical data such as medication, LDLR or APOB gene pathogenic variant, plasma lipid values (triglycerides, total, LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C), family history of cardiovascular disease and general characteristics such as age, sex and date of first visit were collected from the childrens' files. Genetic testing of FH pathogenic variants of all the children was performed by the laboratory of cardiovascular genetics in the Academic Medical Centre, Amsterdam [7].

Pedigree data and clinical data of the FH parents and grandparents of all children were collected. Premature CVD was defined as one of the following: myocardial infarction, proven angina, Coronary Artery Bypass Grafting (CABG) or Percutaneous Coronary Intervention, stroke and peripheral arterial disease in men <55 years and women <60 years [8]. These events were assessed from the patients' medical records and adjudicated by the study team.

Statistics
All data were analysed anonymously using SPSS (version 21.0). Chi-square tests to assess differences in proportions, and the student t-test (since the data were normally distributed) to assess differences in means were used. The values are presented as mean±Standard Deviation (S.D.), unless otherwise specified. Dichotomous variables are presented as numbers and percentages. Statistical significance was defined as $P \leq 0.05$. For the analysis per parent we selected the oldest child.

Results
A total of 292 of 308 consecutive FH children were included in this study. Sixteen subjects were excluded because of FH on clinical grounds. Of the 292 children of 205 parents with FH, 154 were girls. Most children (57%) inherited FH from their father. The majority was Caucasian (94%). Fifty-nine different pathogenic variants were identified. The p.Trp44* pathogenic variant of the LDLR gene was the most prevalent (11%). An APOB pathogenic variant was detected in 8% of the subjects. The average age at first visit to the lipid clinic was 10.6±4.3 years

(range: 0.2-18.0 years). Untreated lipid levels were known of the majority of the children (92%). They had an untreated total cholesterol level of 7.1±1.5 mmol/l and an LDL-C level of 5.4±1.4 mmol/l. Sixty-three percent of the FH children started with a statin after their first visit; 95% of the FH children used a statin at a certain point during follow-up. The mean age of starting statin treatment was 13.6±3.1 years.

Table 1. General characteristics of children with FH

	Children with FH (n=292)	Parent with CVD (n=41)	Parent without CVD (n=164)	p-value
Girls, n (%)	154 (53)			
Maternal inheritance, n (%)	125 (43)			
Paternal inheritance, n (%)	167 (57)			
Dutch Ethnicity, n (%)	273 (94)			
Age (yrs) first visit (mean±SD)	10.6±4.3	12.1±3.9	11.1±4.3	0.39
Age (yrs) started statin (mean±SD)	13.6±3.1	13.9±2.6	14.2±3.2	0.23
DNA pathogenic variants, n (%)	59 (100)			
LDL receptor pathogenic variant	269 (92)			
• p.Trp44*	32 (11)			
• c.313+1G>A	27 (9.2)			
• c.191-2A>G	24 (8.2)			
Apo B gene pathogenic variant	23 (7.9)			
Untreated lipid values 1st visit, mean±SD				
• Total cholesterol (mmol/l)	7.1±1.5			
• LDL-C (mmol/l)	5.4±1.4			
• HDL-C (mmol/l)	1.3±0.3			
• Triglyceride (mmol/l)	1.0±0.5			
Cholesterol lowering Medication				
Medication at 1st visit	2 (1)			
Started medication after 1st visit	180 (63)			
No medication at all	90 (31)			

FH= familial hypercholesterolemia, LDL-C= low density lipoprotein cholesterol, HDL-C= high density lipoprotein cholesterol, CVD= cardiovascular disease

CVD in parents of FH children

A history of CVD was present in 20% (n=41) of the FH parents; 29% (n=33) of the fathers and 9% (n=8) of the mothers. With one exception, all suffered from premature CVD. The mean age of the first event was of 41±8.5 years. In five of these parents (all men), CVD was fatal. Of the grandparents with FH, 49% had a history of CVD, the mean age of their first event was 51±11.1 years. It was not possible to analyse differences in percentage of FH parents with CVD between the first decade (1993-2003) and the second (2004-2014) because of the low number of children visiting the out-patient clinic in the first decade.
Children with a parent without CVD tended to visit the lipid clinic at a younger age than children with a parent with CVD (11.1 vs 12.1 years; p=0.392), but they started statin treatment a bit older (14.2 vs 13.9 years, p=0.231), both not significant.

Table 2. General characteristics of FH parents and FH grandparents

	Parents with FH (n=205)	Paternal (n=114)	Maternal (n=91)	p-value
Inheritance (%)	100	56	44	
Caucasian Etnicity, n (%)	194 (95)	111 (97)	84 (92)	0.18
History of CVD, n (%)	41 (20)	33 (29)	8 (9)	**0.002**
Mortality parent, n (%)	5 (2.4)	5 (4.4)	0 (0)	
Age (yrs) 1st CVD event (mean±SD)	41±8.4	42±8.6	40±8.3	0.54
Untreated total cholesterol (mmol/l)	9.3±1.9	9.4±1.7	9.3±2.1	**0.043**
Index parent	39 (82)	40 (46)	37 (34)	0.88
Grandparents with FH				
History of CVD grandparents	49 (102)			
Age (yrs) 1st CVD event (mean±SD)	51±11.1			

Oldest child per parent selected, CVD= cardiovascular disease, FH= familial hypercholesterolemia

Discussion

Even in the setting of active cascade screening, 1:5 children with FH are identified because their parent experienced CVD, mostly at a premature age. An earlier study from The Netherlands revealed a higher percentage of CVD (31%) in first-degree relatives of genetically confirmed FH children with a similar age and lipid profile compared to our study [9]. This difference might be the result of the effect of nationwide cascade screening. Another explanation could be a referral

bias towards a more severe phenotype as the inclusion of this study took place earlier, 1989-2001 when treating FH children was not common practice.
Compared to other countries, our data are in line with findings from FH children in Norway which also show 21% premature CVD in their parents with FH [10]. In this study children were identified through screening of families with a known mutation or referred to the lipid clinic.
Although not significant, children with a parent without CVD visit the lipid clinic at a younger age than children with parents with CVD (11.1 vs 12.1 years). This finding highlights the result of the active screening program, bringing these children into attention at an early age.
Children with a parent with CVD started with a statin a few months earlier (13.9 vs 14.2 years), suggesting a more proactive treatment in these children. The mean age of starting treatment at 13.6 years is in line with another large cohort of FH children in The Netherlands [11]. Our results show that we don't fulfil the current guideline for screening and starting statin treatment in FH children. Several studies demonstrate atherosclerosis starts already in young children with FH [12], only since 2013 panels and guidelines, recommended that children with suspected FH should be screened between the ages of 5 and 10 years and start with a statin and lifestyle advices about smoking, healthy diet and physical activity when LDL-C levels are >4.0 mmol/l between the age of 8 and 10 years [13, 14].
On the one hand one might argue that the prevalence of 1:5 parents with CVD is high; children ≤18 years should not have a parent with premature CVD. On the other hand a lot of progress has been achieved in the last two decades since grandparents experienced more CVD. Although the grandparents are older, the expectation based on current data is that the percentage CVD in the parents will remain lower. This can mainly be explained due to the efficacy of statin treatment available since 1990 but also through the systematic approach by the cascade screening [3,15]. Patient tailored education and annual follow up by the physician and nurse practitioner of our CVG team working together with the national FH foundation, brings children with FH timely into clinical attention.
This study has a number of limitations. Our data are from a single tertiary referral centre. The majority of our study population is Caucasian, while 21% of Dutch population are non-Caucasian. Therefore we cannot extrapolate our results to other ethnicities. The strength of this study is the complete data collection in a relatively large group of children with FH and their FH parent and FH grandparent.

Conclusions and recommendations

The fact that CVD is still a presenting event of FH in especially fathers, shows that nationwide screening might have been terminated too early. Therefore we recommend to proceed the cascade screening by genetic fieldworkers in The Netherlands as well as in other countries. It ensures that the next generation will be in clinical attention to start statin treatment in time, to prevent CVD.

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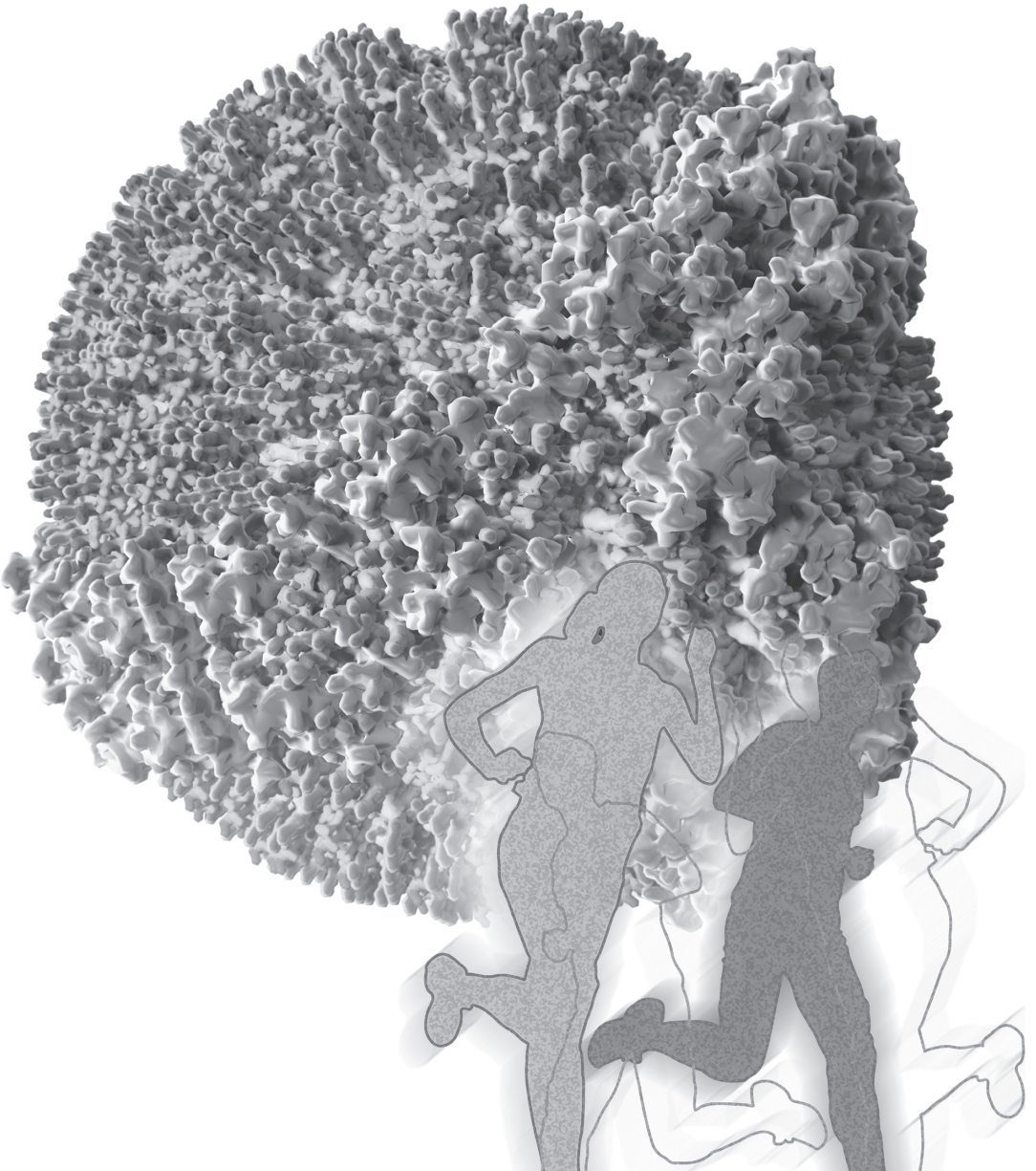

Chapter 4

Cardiovascular risk in patients with familial hypercholesterolemia using optimal lipid lowering therapy

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Abstract

Background

Despite lipid-lowering therapy (LLT), some patients with familial hypercholesterolemia (FH) still develop cardiovascular events. Data about the quantification and factors contributing to this residual risk are lacking.

Objective

This study assessed how many patients with FH developed a cardiovascular event despite LLT and which factors contribute to this risk.

Methods

We performed a time-dependent analysis in a cohort of consecutive heterozygous FH patients using stable LLT to evaluate first and subsequent cardiovascular events. An univariate and multivariate regression analysis was conducted to study the association between clinical characteristics and cardiovascular events.

Results

Of 821 FH patients (median age 47.4 (IQR 35.3-58.3) years) treated with LLT for a median period of 9.5 (IQR 5.1-14.2) years, 102 patients (12%) developed cardiovascular disease (CVD) in 8538 statin treated person years. Patients who developed a cardiovascular event had a median age of 52.0 (IQR 43.8-59.3) years. These patients more often had previous cardiovascular events (32% vs 9%, P<0.001), a family history of premature CVD (58% vs 40%, P=0.001), hypertension (70% vs 22%, P<0.001), higher on-treatment low-density lipoprotein-cholesterol (LDL-C) (162±54 vs 135±58 mg/dL, P<0.001), lower on-treatment high-density lipoprotein cholesterol (HDL-C) (50±15 vs 54±15 mg/dL, P<0.001), and were smokers (32% vs 14%, P<0.001), compared to patients without cardiovascular events. In 31 patients (30%) a subsequent cardiovascular event occurred with a median interval of 5.7 (IQR 2.4-9.3) years between events. They were more often smokers (32% vs 10%, P=0.01) compared to patients with a single cardiovascular event.

Conclusions

Despite LLT FH patients still develop cardiovascular events and especially subsequent events. Classical risk factors such as smoking and hypertension are driving factors for this risk, indicating the high priority of optimizing risk factor reduction in addition to maximum LLT.

Introduction

Familial hypercholesterolemia (FH) is the most common inherited disorder of the lipid metabolism, characterized by elevated levels of plasma low-density lipoprotein-cholesterol (LDL-C). Current studies showed that the prevalence of FH in the Caucasian population is 1:250 [1]. Untreated, 50% of men with FH and 33% of women with FH develop cardiovascular disease (CVD) before 45 years and 60 years of age, respectively [2, 3]. Since three decades statin treatment has been available to lower LDL-C levels. Placebo controlled randomized trials showed that statin therapy leads to a reduced risk of CVD [4]. Although no randomized CVD endpoint trials have been performed in FH patients specifically, observational studies showed that the risk of CVD decreased substantially since FH patients are treated with statins as lipid lowering therapy (LLT) [5, 6]. Therefore statins have been regarded first-line LLT for FH patients [7].

Recently a new class of highly potent LLT has been developed namely Proprotein Convertase Subtilisin / Kexin 9 (PCSK9) inhibitors. The indication of these drugs is restricted to patients at very high CVD risk who do not reach their LDL-C target despite maximum tolerated LLT. FH patients who are not on target using maximum tolerated LLT are considered to correspond to this profile and therefore qualify to use PCSK9 inhibitors according to consensus papers and reimbursement criteria [8, 9]. However data, about the CVD risk among optimal treated FH patients is lacking. Therefore, we assessed in our large cohort of FH patients treated with LLT, how many patients still develop a cardiovascular event despite (optimal) LLT treatment and which factors contribute to the risk of developing a cardiovascular event.

Methods

All FH patients treated with LLT by the Cardiovascular Genetics team at the outpatient lipid clinic of the Erasmus MC, were potentially eligible for this study. Inclusion criteria were: adult patients (age ≥18 years) diagnosed with heterozygous FH who used LLT between 1 January 1989 and April 2016.

The diagnosis heterozygous FH was based on either the identification of an FH causing pathogenic mutation in the LDLR, APOB or PCSK9 gene (genetic FH) or a Dutch Lipid Clinic Network score of ≥6 representative of probable or definite FH (clinical FH) [10].

Cardiovascular risk management and treatment was provided in accordance with the European guidelines on CVD prevention in clinical practice [11, 12]. During every consultation, at least once a year, side effects and adherence of LLT was discussed and lifestyle intervention was advised when necessary.

Clinical data such as LLT, LDLR, APOB and or PCSK9 gene mutations, plasma lipid levels (triglycerides, total cholesterol, LDL-C and high-density lipoprotein cholesterol (HDL-C)), cardiovascular events, family history of CVD and general characteristics (age, sex and date of initiation LLT) were collected from the patients' files and entered in a dedicated database.

Maximum LLT was defined as simvastatin ≥40 mg, atorvastatin 80 mg or rosuvastatin 40 mg, with or without ezetimibe 10 mg. Maximum tolerated LLT was defined as the maximum dose of statins to which patients could tolerate without unbearable side effects in combination with or without ezetimibe. Statin intolerance was defined as documented unbearable side effects of at least three statins including low dose statins on non-daily basis [13]. Target levels for LDL-C were <100 mg/dL for primary and<70 mg/dL for secondary prevention in line with the European guidelines on CVD prevention in clinical practice [7].

Hypertension was defined as blood pressure >140/>90 mmHg on more than two occasions or the use of a antihypertensive medication [14]. Diabetes mellitus (type 1 and 2) was diagnosed according to the American Diabetes Association or the use of anti-diabetic medication [15]. Smoking status was determined by start and stop dates from the patients file. Quit smoking was defined as stopped smoking >1 year.

Cardiovascular events were defined as: myocardial infarction, angina pectoris confirmed by cardiologist, coronary artery bypass grafting or percutaneous coronary intervention, transient ischemic accident or stroke diagnosed by a neurologist or peripheral arterial disease (PAD), diagnosed by vascular surgeon [6]. Cardiovascular events were assessed by a researcher (AGM) from the patients' medical records. Premature CVD was defined as CVD <55 years in men and <60 years in women [6].

The time to cardiovascular events was measured from the date of starting LLT to an event or to the end of study (31 March 2016).

The Medical Ethics Committee of the Erasmus medical Center reviewed the study (MEC 2016-220) and since this study was not subjected to the Dutch Medical Research Involving Human Subjects Act no approval was required. The study was conducted according to the Helsinki Declaration [16].

Statistics

Categorical variables are reported as numbers (percentage) and continuous variables as mean±standard deviation (SD) or median with interquartile ranges (IQR), as appropriate. Normal distribution was tested by the Shapiro-Wilks test. Differences between patients with and without a cardiovascular event after start-

ing LLT were analysed by chi-square and the Student's t-test or Mann Whitney as appropriate. Subsequently, we performed univariate and multivariate logistic regression for analysing the association between clinical characteristics and cardiovascular events during the follow-up period. The multivariate logistic regression model was constructed selecting all significant univariate risk factors and sex. In this model, we adjusted for age, sex, smoking status, body mass index, history of hypertension, family history of premature CVD, history of CVD before starting LLT, HDL-C, LDL-C and triglyceride levels. Smoking status was categorized in never, quit smokers >1 year, and current smokers (current smokers and quit smoking ≤1 year). HDL-C levels were categorized into >39 mg/dL and ≤39 mg/dL, LDL-C levels into <100 mg/dL and ≥100 mg/dL and triglyceride levels into <177 mg/dL and ≥177 mg/dL. Kaplan-Meier curves were computed to evaluate the risk of cardiovascular events over time by status of smoking and history of hypertension. For all tests a p-value (2 sided) less than 0.05 was considered statistically significant.

All data were analysed anonymously using SPSS Statistics for Windows, Version 23.0 (IBM Corp).

Results

We analyzed 821 FH patients (53% women) using LLT, with a median age of 47.4 (IQR 35.3-58.3) years, of whom 75% carried a LDLR or APOB mutation. Baseline characteristics are shown in **table 1** and show that more than half of the total study population (61%) used maximum LLT therapy and 29% used maximum tolerated LLT. Twenty-eight percent of the patients were diagnosed with hypertension, whereas only 4% had diabetes mellitus (64% type 2). Twelve percent experienced a cardiovascular event before LLT was initiated **(table 1)**. The median years of statin use and duration of follow-up was 9.5 (IQR 5.1-14.2) years. In total 102 patients (12%) developed ≥1 cardiovascular event, in 8538 statin-treated person years (16 events per 1000 statin-treated person years), despite LLT for median 6.7 (IQR 2.6-11.7) years. Thirty-one patients developed ≥1 cardiovascular event during LLT. The majority (74%) of the patients had CAD. In one third of the patients who died, the cause of death was cardiovascular, most patients (n=6) died of cancer **(table 2)**.

Patients with genetic FH and clinical FH had a similar risk of developing cardiovascular events. Patients who developed a cardiovascular event were significantly older compared to those who did not develop cardiovascular events (median 52.0 (IQR 43.8-59.3) years vs. 46.9 (IQR 33.3-58.1) years, P=0.001) and started at a later age with LLT (median 43.2 (IQR 36.2-52.2) vs. 34.8 (IQR 22.2-

Table 1. General characteristics of FH patients according to CV event at maximum tolerated LLT

Characteristics	Total n=821	CV event on LLT n=102 (12%)	No CV event on LLT n=719 (88%)	p
Age* (years) median (IQR)	47.4 (35.3-58.3)	52.0 (43.8-59.3)	46.9 (33.3-58.1)	**0.001**
Women, n(%)	437 (53)	48 (47)	389 (54)	0.20
Caucasian ethnicity, n(%)	766 (93)	93 (91)	673 (94)	0.39
Cardiovascular risk factors, n(%)				
• Ever smoker	356 (43)	67 (66)	289 (40)	**<0.001**
• Current smokers*	130 (16)	33 (32)	97 (14)	**<0.001**
• BMI mean±SD	26.5±4.6	27.9±4.1	26.3±4.6	**0.002**
• Hypertension	232 (28)	71 (70)	161 (22)	**<0.001**
• DM type 1 and 2	36 (4)	13 (13)	23 (3)	**<0.001**
• Family history premature CVD	347 (42)	60 (59)	287 (40)	**<0.001**
• History of CVD before LLT	95 (12)	33 (32)	62 (9)	**<0.001**
FH genetic mutation, n(%)				
• LDL receptor mutations	552 (67)	68 (67)	484 (67)	0.91
• Apo B mutation	65 (8)	10 (10)	55 (8)	0.43
FH clinical criteria	204 (25)	24 (24)	180 (25)	0.81
Lipid lowering therapy* n(%)				
• Rosuvastatine	300 (37)	25 (25)	275 (38)	
• Atorvastatine	300 (37)	39 (38)	261 (36)	
• Simvastatin	170 (21)	36 (35)	134 (19)	
• Pravastatin	16 (2)	2 (2)	14 (2)	
• Fluvastatin	6 (1)	0	6 (1)	
• Ezetimibe monotherapy	11 (1)	0	11 (1)	
Intolerant; no statin	29 (4)	0	29 (4)	**0.040**
Maximum LLT	498 (61)	67 (66)	431 (60)	0.28
Maximum tolerated LLT	240 (29)	26 (26)	214 (30)	0.42
Treated Lipid values*, mean±SD				
• Total-Cholesterol (mg/dL)	209±62	232±58	205±62	**<0.001**
• LDL-Cholesterol (mg/dL)	139±58	162±54	135±58	**<0.001**
• HDL-Cholesterol (mg/dL)	54±15	50±15	54±15	**<0.001**
• Triglyceride (mg/dL)	115±62	142±89	115±62	**0.001**
LDL-C reduction >50%, n(%)	344 (42)	30 (30)	314 (44)	**0.009**
LDL-C <135 mg/dL, n(%)	501 (61)	34 (34)	467 (65)	**<0.001**
LDL-C <100 mg/dL, n(%)	153 (19)	9 (10)	144 (21)	**0.008**

*BMI= body mass index; CVD= cardiovascular disease; DM= diabetes mellitus; HDL= high density lipoprotein; LDL=low density lipoprotein; LLT= lipid lowering therapy *At first event or 31-03-2016*

Table 2. Cardiovascular outcomes in FH cohort during median 6.7 years of lipid lowering therapy

Cardiovascular outcomes	Total Cohort n=821
All-cause mortality, n	12
• Cardiovascular mortality	4
• Cancer	6
• Other	2
Cardiovascular events, n(%)	102 (12)
Coronary artery disease, n(%)	75 (74)
• Myocardial infarction	36 (35)
• Angina pectoris	12 (12)
• PCI/CABG	27 (27)
Cerebro-vascular events, n(%)	23 (23)
• TIA	13 (13)
• Stroke	10 (10)
Peripheral vessel disease, n(%)	4 (4)
• PAD	4 (4)

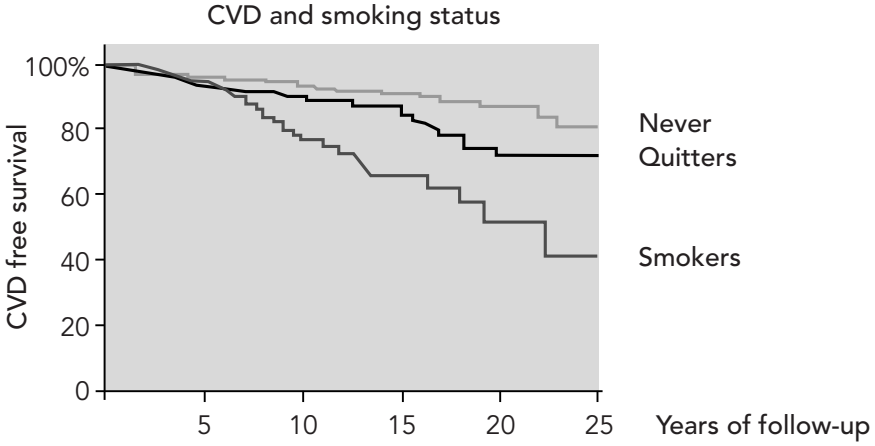
CVD= cardiovascular disease; PCI= percutaneous coronary intervention; CABG= coronary artery bypass grafting; TIA= transient ischemic accident; PAD= peripheral arterial disease

47.2 years, P<0.001). Patients with CVD during LLT had more classical cardiovascular risk factors such as smoking (32% vs 14%, P<0.001), hypertension (70% vs 22%, P<0.001), diabetes mellitus (13% vs 3%), a higher body mass index (27.9±4.1 vs 26.3±4.6, P=0.002), more often a history of CVD before LLT initiation (32% vs 9%, P<0.001) and a family history of premature CVD (59% vs 40%, P<0.001). Moreover, treated total cholesterol, LDL-C and triglyceride levels were higher and HDL-C was significantly lower in patients who developed a cardiovascular event compared to those who did not develop a cardiovascular event. The treatment goal of LDL-C <100 mg/dL or LDL-C <135 mg/dl as well as LDL-C reduction ≥50% was less often achieved in patients who developed a cardiovascular event CVD **(table 1)**. Of the 344 patients who achieved LDL-C reduction ≥50%, 30 (9%) developed a cardiovascular event and of the 472 patients who had an LDL-C reduction of <50%, 72 (15%) developed a cardiovascular event. Of the 501 patients who achieved an LDL-C <135 mg/dL of these 34 (7%) developed a cardiovascular event and of the 317 patients with an LDL–C ≥135 mg/dL of these 68 (21%) developed a cardiovascular event.

Of all variables 11 significant determinants were identified for the multivariate model **(table 3)**. Seven determinants were independently associated with the occurrence of cardiovascular events. In addition to age, current smoking, history of hypertension, family history of CVD, history of CVD before starting LLT, treated lipid levels; high LDL-C and low HDL-C remained in the model. The analysis including age at initiation of LLT showed identical results. Current smokers (n=130, 16%) had a 4 times (OR 4.24; 95% CI 2.14-8.37) increased risk of developing a cardiovascular event and therefore a lower CVD-free survival compared to patients who never smoked, or those who quit smoking **(table 3, figure 1)**. Furthermore, patients with hypertension had an almost 3 times higher risk of developing cardiovascular events (OR 2.95; 95% CI 1.68-5.18) and consequently a lower CVD-free survival **(table 3, figure 2)**. Other factors associated with an cardiovascular event were CVD prior to the start of LLT (OR 2.47; 95% CI 1.34-4.57), a family history of premature CVD (OR 1.85; 95% CI 1.10-3.11), higher LDL-C levels (OR 3.64; 95% CI 1.60-8.29) and lower HDL-C levels (OR 4.27; 95% CI 2.18-8.36).

Thirty percent (n=31) of the treated patients with a first cardiovascular event experienced a subsequent event after a median of 5.7 (IQR 2.4-9.3) years at a median age of 58.6 (IQR 48.7-65.6) years with a median treatment duration of 12.3 (IQR 9.0-16.8) years. Patients, who developed a subsequent cardiovascular event, were more often current smokers (32% vs 10%, P=0.01) and showed a

Figure 1. CVD free survival of FH patients and smoking status



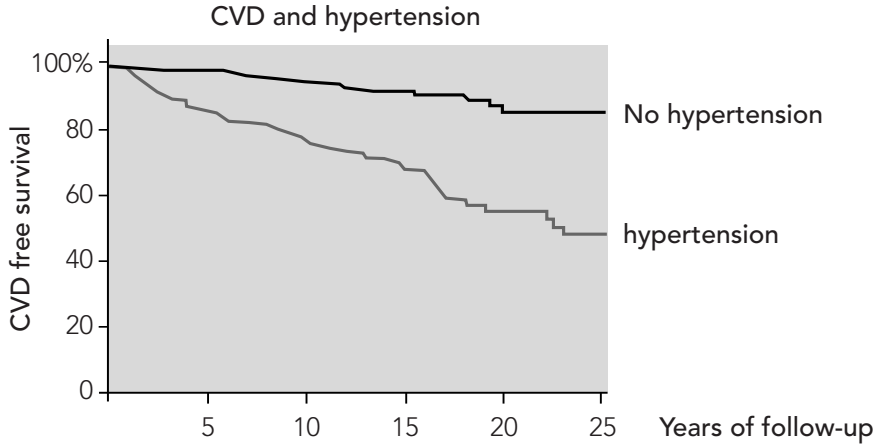
N, never Smokers	463	324	177	78	40	12
N, at risk Quitters	225	168	118	56	33	12
N, at risk Smokers	130	87	42	23	9	2

Table 3. Associations between determinants and cardiovascular events

Characteristics	Univariate (OR, 95%CI)	P	Adjusted* (OR, 95%CI)	p
Age (years)	1.07 (1.05-1.08)	<0.001	1.07 (1.04-1.10)	**<0.001**
Sex	0.75 (0.50-1.14)	0.18	1.07 (0.62-1.84)	0.82
Cardiovascular risk factors				
Never smokers	1		1	
Current smokers	4.18 (2.48-7.06)	<0.001	4.24 (2.14-8.37)	**<0.001**
Quit smokers >1 year	2.18 (1.32-3.59)	0.002	1.21 (0.66-2.20)	0.54
DM type 1 and 2	4.39 (2.15-8.97)	<0.001	2.32 (0.98-5.52)	0.06
BMI	1.07 (1.03-1.12)	0.001	1.01 (0.96-1.07)	0.71
Hypertension	7.94 (5.03-12.54)	<0.001	2.95 (1.68-5.18)	**<0.001**
Family history premature CVD	2.15 (1.41-3.28)	<0.001	1.85 (1.10-3.11)	**0.021**
History of CVD before LLT	5.07 (3.11-8.27)	<0.001	2.47 (1.34-4.57)	**0.004**
Treated lipid levels				
Triglyceride >177 mg/dL	1.95 (1.13-3.36)	0.016	0.71 (0.36-1.43)	0.34
HDL-cholesterol <39 mg/dL	3.80 (2.36-6.13)	<0.001	4.27 (2.18-8.36)	**<0.001**
LDL-cholesterol >100 mg/dL	2.47 (1.21-5.03)	0.013	3.64 (1.60-8.29)	**0.002**

BMI= body mass index; CVD= cardiovascular disease; DM= diabetes mellitus; LLT= lipid lowering therapy; LDL=low density lipoprotein; HDL= high density lipoprotein
**Adjusted for: age, sex, smoking, DM, BMI, history of hypertension, family history of CVD, history of CVD before starting LLT, triglyceride, high LDL-C, low HDL-C.*

Figure 2. CVD free survival of FH patients and hypertension



N, no hypertension	587	419	232	104	51	21
N, at risk hypertension	231	161	102	52	31	12

trend towards more often having (history) hypertension (84% vs 63%, P=0.06), compared to those who remained without a subsequent cardiovascular event. However LDL-C levels were similar among these groups (P=0.54) **(table 4)**.

Table 4. Characteristics of FH patients using lipid-lowering therapy who did and who did not develop a second cardiovascular event

Characteristics	Second event on LLT n=31	No second event on LLT n=71	p
Age* (years) median (IQR)	58.6 (48.7-65.6)	57.1 (48.4-66.6)	0.82
Women, n(%)	13 (42)	35 (49)	0.53
Caucasian ethnicity, n(%)	26 (84)	67 (94)	0.13
Cardiovascular risk factors, n(%)			
• Current smokers*	10 (32)	7 (10)	**0.011**
• BMI, mean±SD	27.4±4.3	28.1±4.0	0.44
• Hypertension	26 (84)	45 (63)	**0.060**
• DM	4 (13)	9 (13)	1.0
• Family history premature CVD	19 (61)	41 (58)	0.83
• History of CVD before LLT	12 (39)	21 (30)	0.37
FH genetic mutation, n(%)			
• LDL receptor mutations	20 (65)	48 (67)	0.82
• Apo B mutation	4 (13)	6 (9)	0.49
FH clinical criteria	7 (23)	17 (24)	1.00
Lipid lowering therapy* n(%)			
• Rosuvastatine	5 (16)	41 (58)	<0.001
• Atorvastatine	17 (55)	17 (24)	0.003
• Simvastatin	7 (23)	8 (11)	0.22
• Pravastatin	1 (3)	0 (0)	n.a.
• Fluvastatin	0	1	n.a.
• Ezetimibe monotherapy	0	1	n.a.
Intolerant; no statin	1 (3)	4 (6)	n.a.
Maximum therapy, n(%)	19 (61)	49 (69)	0.50
Maximum tolerated therapy, n(%)	9 (29)	18 (25)	0.81
Treated lipid levels*, mean±SD			
LDL-cholesterol (mg/dL) mean±SD	147±62	139±62	0.54
LDL-C <70 mg/dL, n(%)	1 (3)	6 (9)	0.67
LDL-C <100 mg/dL, n(%)	6 (20)	17 (24)	0.80

*LDL= low density lipoprotein; CVD= cardiovascular disease; BMI= body mass index; DM= diabetes mellitus; LLT= lipid lowering therapy * At second event or 31-03-2016*

Discussion

Our results show that despite maximum (tolerated) LLT, 12% of our FH patients developed a cardiovascular event. Modifiable factors associated with this residual CVD risk were smoking and hypertension as well as LDL-C levels and HDL-C levels. Among patients who developed an event despite LLT, 30% developed a subsequent cardiovascular event, which was also associated with smoking.

Although observational studies showed that LLT reduces CVD in FH patients, data on the quantification of the residual risk of CVD in LLT-treated FH patients is sparse. Cross-sectional studies in FH patients using LLT reported the prevalence of CVD between 9-22% [17-19]. Only one study, a Spanish cross-sectional cohort, reports about second cardiovascular events among FH patients. In this study the proportion of women who developed a subsequent cardiovascular event was similar to our study (27% vs. 28% respectively). However, in the Spanish cohort much more men developed a subsequent event compared to our study (60% vs 33%, respectively) [19]. In all aforementioned cross-sectional studies no information was provided whether these cardiovascular events occurred before the initiation of LLT or during LLT.

Previously two Dutch studies reported the cumulative event-free survival comparing FH patients using statins versus no statin treatment. These studies showed a residual risk of CVD of 11 per 1000 patient years on low-dose statin therapy and 8.8 per 1000 person-years using moderate-to-high-statin therapy [5, 18]. The study of Versmissen et al., performed a model in which statin-treatment was used as a time-dependent variable, mimicking a randomized clinical trial [5]. Besseling, et al. coupled data from the Dutch national FH screening program to the Pharmo RLS databases which included the national registry on mortality and hospitalization as well as in-and out-patient pharmacies to assess the residual risk of CVD in FH patients. No individual hospital records were available and risk factors were self-reported. In the final analysis only 2.46% of the total FH population could be analysed by this linkage and patients included in the final analysis had a more unfavourable risk profile compared to patients who were not included [20]. Therefore a selection bias cannot be excluded. Our study differs from the aforementioned studies because our aim was not to compare CVD risk of FH patients with and without LLT, but to focus upon the variation of CVD among FH patients using long-term LLT as the benefit of LLT in this population is considered evident.

Both genetic and lifestyle factors contribute to the risk of CVD [21, 22]. Similar to the general population not only LDL-C but also other risk factors such as smoking, hypertension, diabetes mellitus, elevated lipoprotein(a) and low HDL-C le-

vels have been associated with CVD in FH patients. Previously Jansen et al. showed in a large FH cohort study that classical risk factors such as smoking and hypertension were independent predictors for developing CVD [23]. In contrast to the current study it was not recorded when and if LLT was initiated. Also, in our FH study population, classical non-lipid risk factors such as hypertension and especially smoking, were independent risk factors for developing cardiovascular events. An important observation is the beneficial effect of those who stopped smoking, had a lower risk of CVD. This risk was almost comparable to never smokers. In our population of treated FH patients, 18/33; 55% stopped smoking after a cardiovascular event. Although this seems disappointing, the result is in line with the EUROASPIRE study in which 51% ceased to smoke after a cardiovascular event [24]. Sadly thus far, the success of stop smoking programs in adults is limited [25]. Therefore, in our opinion for optimal CVD prevention, intensified lifestyle intervention with a focus on smoking cessation irrespective of a cardiovascular event remains crucial [26]. Collaboration with professional partners dedicated to stop-smoking and lifestyle intervention can improve cardiovascular risk management [27].

In addition to classical risk factors, LDL-C levels not on target, and low HDL-C levels were also associated with cardiovascular events in those patients who developed a first cardiovascular event during LLT. Previous studies showed that only a small percentage of FH patients reached target LDL-C levels. In the cohort of Pijlman et al., only 21% of the FH patients reached LDL-C target levels [17]. Among the factors affecting the low level of LDL-C goal attainment are patient-related factors such as statin side effects and insufficient adherence on the one hand, and on the other, laxity of healthcare professionals to start or adequately up-titrate LLT. Lastly, in patients with very high untreated LDL-C levels, maximum LLT consisting of high dose statin in combination with ezetimibe is often not sufficient to reach LDL-C targets [17]. In our population the majority of patients used either maximum LLT (61%) or maximum tolerated LLT (29%) and in a subset of these patients we previously showed that the adherence of our patients was as high as 89% [28]. However, still only 19% of our patients reached an LDL-C level of <100 mg/dL.

Increased levels of lipoprotein(a) [Lp(a)] are an independent risk factor of CVD [29]. Patients with FH have higher Lp(a) levels compared to non-FH subjects. Current lipid-lowering therapy such as statins and ezetimibe do not reduce Lp(a). Therefore it is not unexpected that increased Lp(a) concentrations have been associated with residual CVD risk both in FH and non-FH patients [30]. A problem with Lp(a) measurement is the standardization of the used immune-assays. During

follow-up several different assays have been used in our out-patient clinic which are not comparable and were mostly not isoform independent. Therefore it was not possible to assess the effect of Lp(a) on the residual risk in our study.
The new class of lipid-lowering medication, PCSK9 inhibitors lower LDL-C on average 54% compared to placebo, in addition to LLT [31]. Recently, the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial showed an additional 59% reduction in LDL-C and a reduction of 15% in composite CVD outcome in patients using evolocumab compared to placebo [32]. Randomized controlled trials in FH patients showed a 43-66% reduction in LDL-C levels [33, 34]. Reimbursement criteria differ internationally, but in general the costly PCSK9 inhibitors are reserved to patients who have the highest risk of CVD despite current LLT [35].
The current study reveals a clear contribution of classical risk factors which are partly modifiable in a consecutive cohort of present-day FH patients using LLT with detailed follow-up data. Therefore, in our viewpoint, clinicians should not solely focus on lipid parameters such as LDL-C but also pay attention to classical risk factors such as smoking and hypertension. Initiation of PCSK9 inhibitors will not become the solution to eradicate CVD risk in this population as long as other risk factors are not treated. Consequently, we propose a multifactorial approach for treatment of FH patients evidently optimizing maximal LLT, but without disregarding to concentrate on non-lipid risk factors.
Our study has several strengths and limitations. This is the first study with statin-years in a systematically well-phenotyped cohort of FH patients using long-term LLT to determine the contribution of additional risk factors of CVD identifying individuals at high risk. Because our study included a follow-up duration of many years we had to take several cardiovascular disease prevention guidelines into account. Until 2007 the European CVD prevention guideline with an LDL-C treatment goal in primary prevention was ≤3.5 mmol/l, subsequently an LDL-C of ≤2.5 mmol/l was advised. Moreover, we present a single-centre cohort in a specialized tertiary hospital, therefore external validation is not ensured. Finally, lipoprotein(a) levels, a lipid factor often associated with residual cardiovascular risk, was not available for a large number of patients and could therefore not be evaluated.

Conclusions and recommendations

Despite long-term optimal LLT, 12% of our FH patients developed a cardiovascular event. In addition to lipid parameters, classical risk factors, especially smoking and hypertension, contributed to the cardiovascular events. Moreover,

almost one third of statin-treated FH patients with a cardiovascular event developed a subsequent event associated with smoking and hypertension, underlining the need for improved CVD prevention. Treatment of FH patients should, therefore, not only focus on optimizing LDL-C levels, but also on improving other CVD risk factors.

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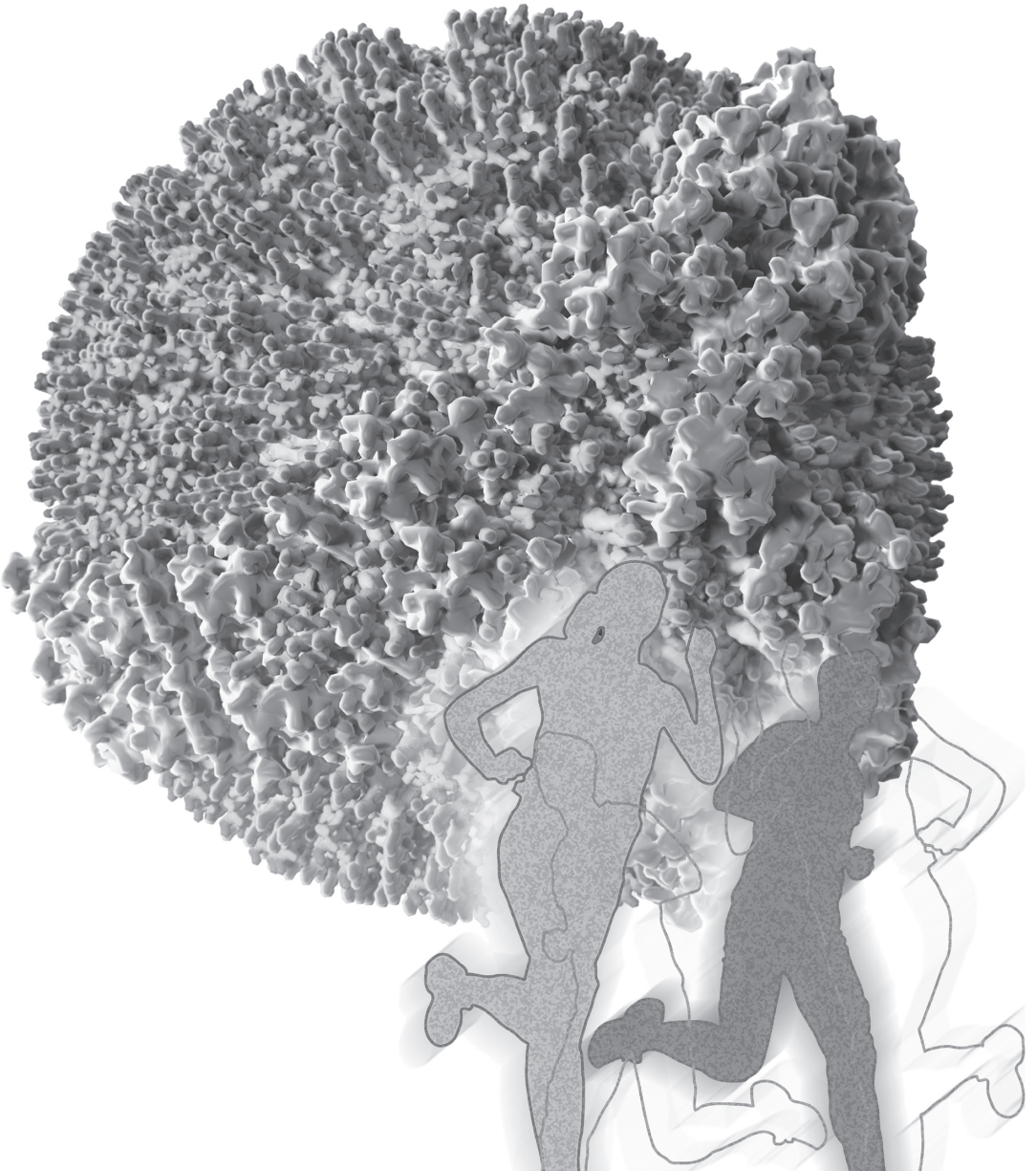
Part 2

Management of familial hypercholesterolemia



Chapter 5

Predicting non-adherence in patients with familial hypercholesterolemia

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Abstract

Purpose

Familial hypercholesterolemia (FH) is an autosomal dominant disorder, associated with a high risk of premature coronary heart disease (CHD). CHD prevention consists of lifestyle changes combined with lifelong statin treatment. Good adherence to statins reduces the risk of events substantially. This study was designed to identify determinants of non-adherence and to develop a model predicting non-adherence.

Methods

A single centre survey including all consecutive heterozygous FH patients above age 18 years, who were treated by a specialized team in the outpatient clinic of a university hospital in The Netherlands between 2008 and 2009. In addition to clinical data, patients completed a questionnaire concerning medication adherence.

Results

We analyzed 321 patients (169 women) with a statin prescription, whose mean age was 46±14 years (± SD) and 13% of the patients had CHD. The untreated mean total cholesterol was 10±2.3 mmol/l. On average patients were 10 years on cholesterol-lowering therapy (range 1-29 years). Adherence was reported by 89% of the patients (>90% adherence). Non-adherence was associated with younger age (OR=10.64, 95% CI 2.86-39.68), high total cholesterol level during prescription (OR=4.29, 95% CI 1.86-9.89) and a relatively low untreated total cholesterol level (OR= 3.94 95% CI 1.39-11.14). A prediction model based on these three determinants had a c-index of 0.78 and a calibration with P=0.88.

Conclusion

Based on three independent determinants, a prediction model is developed to identify non-adherent FH patients. This model needs to be tested in future prospective research. It might be a first step in improving statin adherence in this extremely high risk group.

Introduction

Familial hypercholesterolemia is associated with a severe risk of coronary heart disease [1, 2]. Effective CHD prevention is available consisting of lifestyle changes and lifelong statin treatment [3-6]. Remarkably, the efficacy of statin treatment of FH patients was much larger than observed in most large primary prevention trials; 76% versus approximately 37% CHD risk reduction, respectively [7-9].

Non-adherence with prescribed drug regimens is a pervasive medical problem. Adherence rates are low in patients with chronic diseases [10]. Obviously, non-adherence is a threat to effective cardiovascular prevention in FH patients. Statin treatment can be considered as therapy in the causal pathway of FH, therefore good adherence is a necessity. In primary prevention studies in patients with hypertension and diabetes, only half of the patients took at least 80% of the prescribed statin dosage after one year of follow-up. Clearly, the retention in treatment decreases over time [11]. Adherence is defined as 'the extent to which patients follow the recommendations by their healthcare professional' [12]. In the present study, we specifically focus on the treatment with statins.

A large number of predictors of poor adherence to different medications have been described that may also apply to statins: primary prevention, low level of education, low socioeconomic status, psychological problems particularly depression, side effects, patient's lack of belief in benefit, complexity of therapy especially the start of co-medications, age and a low rate of control appointments [4, 13-17]. Although several studies described the aforementioned predictors of non-adherence, it is not known whether these predictors have a similar impact in the FH population. The majority of FH patients in The Netherlands are identified through family screening in order to start treatment early in adulthood. Therefore, our patients are relatively young and mostly asymptomatic. On the one hand one might argue that offering lifelong treatment to asymptomatic persons is unlikely to obtain high adherence. On the other hand a lot attention has been paid to the high morbidity scores linked to reduced adherence in particular of statins [18, 19].

There is potentially much to be gained by improving adherence. A number of possibilities could be considered. Motivational interviewing [20, 21], the Medication Electronic Monitoring System (MEMS) and strategies for enhancing self-efficacy are options [22-25]. However non-adherence has to be recognized first. Healthcare professionals do not have many opportunities to identify non-adherence with confidence. The goal of our study was to develop a prediction model for identification of FH patients who do not adhere with statin use.

Patients and methods

Participants

Our tertiary referral centre treats patients with cardiovascular diseases and different types of inherited lipid disorders. The majority of patients (70%) referred between 1 January 2008 and 31 December 2009, were diagnosed with FH. All consecutive adult patients with heterozygous FH were considered eligible for inclusion in this study. The diagnosis FH was based on either the identification of an FH causing mutation (in the LDL-receptor or Apo B gene) or on the following clinical criteria: LDL cholesterol level >the 95th for age and gender specific percentile in combination with at least one the following; presence of xanthomas, LDL cholesterol >95th percentile for age and sex in a first degree relative or premature CHD in a first degree relative (defined as male <55y, female <60y). The criteria of Aalst–Cohen were used [26].

The medical ethical committee of our institute approved the protocol and all participants gave written informed consent.

Study design

All patients were carefully monitored annually at the lipid clinic by a specialized vascular nurse, according to the European guideline for the management of dyslipidaemias [3]. Side effects were discussed and statins were changed when necessary. Clinical data was collected from the patients' files.

The development of the questionnaire occurred in cooperation with experts from the Cardio Vascular Genetic (CVG) team. Patients were asked how often they deviated from the medication regime. They could choose one of the following options; option 1 was never, 1-2 times in a year; option 2 was rarely, 1-4 times in a quartile; option 3 was regularly, 1-2 times in two weeks; and option 4 was often, 3 or more times in one week. We defined adherence as the use of the prescribed medication for more than 90% of the time (option 1 and 2) and non-adherence as less than 90% (option 3 and 4).

The questions focusing on not taking statins originate from the Medication Adherence Report Scale (MARS) which has a good reliability [27].

Hypertension and diabetes mellitus were mentioned as relevant co-morbidities. Hypertension was defined as blood pressure >140/>90 mmHg on more than 2 occasions or the use of a prescribed antihypertensive medication and type 2 diabetes mellitus was diagnosed according to WHO criteria or the use of prescribed anti-diabetic medication [28].

Statistical analysis

All data were analysed anonymously by SPSS (version 17.0). Chi-square tests to assess differences in proportions, and the student t-test to assess differences in means were used. The values are presented as mean±Standard Deviation (S.D.), unless otherwise specified. Dichotomous variables are presented as numbers and percentages. Statistical significance was defined as $P \leq 0.05$.

For the prediction model, to estimate non-adherence, univariate and multivariate analysis were used for variable selection. Univariate logistic regression analysis was applied to study the relation between potential predictors for non-adherence. In addition to age and gender the 4 most significant variables in the univariate analysis, based on Wald $\chi 2$ test, were included in the multivariate analysis. Only 4 additional variables were added with respect to the limited numbers of patients [29].

The multivariate logistic regression model was constructed using backward elimination of the least significant variables until all variables in the model had a p-value ≤0.15. We accepted a type I error of 15% for all variables. Subsequently, a risk score to predict non-adherence (adherence <90%) was developed, which included all relevant risk factors, which were weighted according to the natural logarithm (Ln) of the corresponding odds ratio (OR). Age, untreated and treated total cholesterol were categorized in: age 18 to 35, 36 to 50, and ≥51 years; untreated total cholesterol <8 mmol/l, 8 to 10 mmol/l and >10 mmol/l; treated total cholesterol <5 mmol/l and ≥5 mmol/l.

The performance of the final model was studied with respect to discrimination, as indicated by the C-index and calibration, as shown with the Hosmer-Lemeshow goodness-of-fit test for predicted versus observed probabilities.

Results

A total of 321 out of 407 consecutive FH patients were included in the present study. A minority of the outpatient clinic population was not included in the study; n=26 did not gave informed consent, n=16 returned the questionnaire after the deadline and n=44 did not fulfil the inclusion criteria. Of those patients 30 had an age below 18 years, 3 were pregnant, 3 had a normal cholesterol (LDL cholesterol <3 mmol/l), 1 patient just recently started statin treatment and 7 patients were without statins because of severe side effects on prior prescriptions. The baseline characteristics of the FH population and their adherence are shown in **table 1**. The response rate of the questionnaire was 90%. Statins reduced the untreated total cholesterol level with 45.5 %. Of the patients with a treated LDL-C ≥2.5 mmol/l (n=108), either the treating physician was satisfied

Table 1. Characteristics of patients according to adherence

	% n=321	Adherent (>90%) 89% n=285	Non Adherent (<90%) 11% n=36	p
Age (years)	45.6±13.9	47±13.8	38±12.1	**<0.01**
Women	52.6 (169)	53 (151)	50 (18)	0.7
Cardiovascular risk factors				
Smokers (current)	15.6 (50)	14 (41)	25 (9)	0.1
Hypertension	15.6 (50)	17 (48)	11 (4)	0.8
Diabetes	3.1 (10)	4 (10)	0 (0)	0.9
History of CVD	12.8 (41)	14 (40)	3 (1)	0.09
Family history premature CHD	46.1 (148)	50 (142)	42 (15)	0.4
FH diagnosis				
LDL receptor gene mutation	72.4 (232)			
Apo B gene mutation	5.5 (18)			
Clinical grounds	22.1 (71)			
Side effects never	45.8 (147)	46 (132)	42 (15)	0.60
Side effects current statin	27.4 (88)	28 (81)	19 (7)	0.3
Body Mass Index (kg/m2)	26.1±4.4	26±4.3	26±5.1	0.9
Statin use (years)	9.8±6.9	10.2±7.0	6.4±4.4	**0.01**
Untreated total cholesterol	10.0±2.3	10.1±2.3	9.0±2.1	**0.01**
Treated lipid values				
Total cholesterol	5.2±1.3	5.2±1.2	6.0±1.8	**<0.01**
LDL cholesterol (mmol/l)	3.4±1.1	3.3±1.0	4.1±1.6	**<0.01**
HDL cholesterol (mmol/l)	1.3±0.4	1.3±0.4	1.2±0.3	0.09
Triglyceride (mmol/l)	1.17±0.6	1.1±0.6	1.3±0.6	0.07
LDL= low density lipoprotein				
HDL= high density lipoprotein				
CHD= coronary heart disease				
CVD= cardiovascular disease				

LDL low density lipoprotein, HDL high density lipoprotein, CHD coronary heart disease, CVD cardiovascular disease.

with an LDL-C under 2.8 mmol/l (n=14), or patients could not tolerate a higher dose or stronger statin (n=35) or the statin therapy was in the up-titration phase (n=59). The treatment goal for LDL-C <2.5 mmol/l was only achieved in 18.7% of the patients. Nearly 40% of the patient's LDL-C was above 3.5 mmol/l. Maximum therapy was prescribed in more than half of the patients (58.3%, n=187). Patients on maximum therapy achieved the treatment goal in 18.2%.

Table 2. Associations between determinants and non-adherence

	Crude OR (95%CI)	Adjusted OR (95%CI)	p
Women	0.89 (0.44-1.76)		
Age (years)	0.95 (0.93-0.98)		
18 – 35	7.80 (2.50-24.36)	10.64 (2.86-39.68)	**<0.01**
36 – 50	4.53 (1.47-13.99)	7.06 (1.95-25.48)	**<0.01**
≥51	1	1	**<0.01**
Statin use (years)	0.90 (0.84-0.97)		
Untreated total cholesterol			
<8 mmol/l	3.57 (1.43-8.88)	3.94 (1.39-11.14)	**0.01**
8-10 mmol/l	1.45 (0.63-3.32)	1.69 (0.68-4.16)	0.3
>10 mmol/l	1	1	**0.04**
Treated total cholesterol			
≥5 mmol/l	1.47 (1.17-1.84)	4.29 (1.86-9.89)	**<0.01**
<5 mmol/l	1	1	
LDL cholesterol (mmol/l)	1.63 (1.26-2.10)		

Non-adherence, using less than 90% of the prescribed medication, was reported by 11% of the patients. They were significantly younger than adherent patients (38±12.1 vs. 47±14.0 years; p<0.001) and shorter on statin prescription (6.4±4.4 vs. 10.2±7.0 years; p=0.005). As expected, they had on average higher LDL-C levels than adherent patients (4.1±1.6 vs. 3.3±1.0 mmol/l; p<0.001). Their treated total cholesterol was almost 1 mmol/l higher (6.0±1.8 vs. 5.2±1.2 p=0.001), despite lower untreated total cholesterol levels (9.0±2.1 vs. 10.1±2.3).
Potentially relevant determinants of non-adherence were tested in a univariate analysis model for non-adherence in individual FH patients **(table 1)**. All reasons mentioned by the patients for being non-adherent, were having side effects, being not at home, lack of drugs, aversion of medication or no time to take medication. These answers were non-significant in de univariate analysis (data not shown).

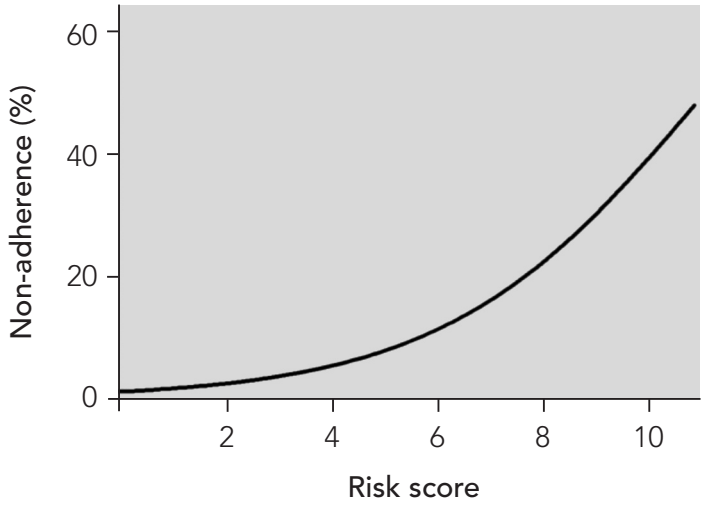
A total of 6 determinants were selected for a multivariate model **(table 2)**. Three independent determinants for non-adherence were identified: age, untreated total cholesterol and treated total cholesterol remained in the model. Patients younger than 36 years (n=77, 24%) were almost 10 times (OR 10.64; 95% CI 2.86-39.68) more non-adherent than patients older than 51 years (n=121, 38%). Pa-

tients with an untreated baseline cholesterol below 8 mmol/l were 4 times more (OR 3.94; 95% CI 1.39-11.14) non-adherent than patients with an untreated cholesterol above 10 mmol/l. Patients with a treated cholesterol above 5 mmol/l were 4 times (OR 4.29; 95% CI 1.86-9.89) more frequent non-adherent as well. The non-adherence risk score was based on the natural logarithm of the OR's of the variables in the final multivariable model, presented in **table 3**. The c-index for the multivariable non-adherent model was 0.78. The Hosmer-Lemeshow goodness-of-fit test was not significant (P = 0.88). Adding all appropriate points from the variables results in a non-adherence risk score (0-11 points) with an increasing chance of non-adherence with a higher score. In **figure 1**, the risk score for non-adherence is shown.

Table 3. Non-adherence risk score

Characteristics	Multivariate	Contribution to the non-adherence risk score
	Ln OR (95% CI)	Points
Untreated cholesterol <8 mmol/l	1.37	3
Untreated cholesterol 8-10 mmol/l	0.52	1
Untreated cholesterol >10 mmol/l	-	0
Age 18 -35 years	2.37	5
Age 36 -50 years	1.95	4
Age ≥51 years	-	0
Treated total cholesterol		
≥5 mmol/l	1.46	3
<5 mmol/l	-	0 +
Add the points to obtain the risk score		0-11

Figure 1. Non-adherence risk score



Discussion

Our results demonstrate that statins reduced the untreated total cholesterol level with 45.5% in our heterozygous FH study population. In only 19% of patients the treatment goal was achieved. We assessed whether these results were influenced by the factor non-adherence. Non-adherence of statins was reported in 11% of the patients. They were younger and shorter on statin prescription. They showed higher treated LDL-C and total cholesterol levels and had lower untreated baseline cholesterol. Based on these independent variables, a non-adherence risk score calculator was developed.

The treated lipid values of our cohort are in line with a large cross-sectional study in The Netherlands, which also revealed a significant reduction of cholesterol levels in patients with FH [30]. In the present study, the FH population is expected to have a higher increased risk for CVD, based on the higher percentage of patients with a genetic diagnosis of FH compared to the aforementioned study (78% versus 54%, respectively). Only a small percentage of patients (19%) reached the treatment goal of LDL-C <2.5 mmol/l for primary cardiovascular prevention, despite maximum statin therapy in almost 60%. More importantly, 13% of these patients, with a mean age of 46 years, had a history of a cardiovascular event. The low percentage of patients on target can mainly be explained by insufficient availability of strong enough cholesterol-lowering drugs

for FH patients. Yet, non-adherence should not be underestimated as factor for decreasing the effectivity of statins. Data from a review of Bates et al. showed a high frequency of statin non-adherence in several primary prevention studies [31]. High adherence should be achieved since the incidence of nonfatal CAD events can decrease substantially, if 90% of the prescribed statin is used for at least one year [11, 32, 33]. Although the monitoring of lipid lowering treatment is recommended by several clinical guidelines, the competence to recognize non-adherence by physicians appears poor [10, 34.] In addition, knowledge of causes of non-adherence is essential for managing patients on any medication [31]. In order to be able to identify patients at risk for non-adherence, a prediction model was developed.

This prediction model can be used in clinical practice during patient consultation to assess and improve adherence. The variables in the model are available in daily practice. If patients are at risk for non-adherence according to the model, it should be discussed and guidance and support can be provided by healthcare prescribers. For example, a 24-year-old man with an untreated total cholesterol of 7.5 mmol/l and a treated total cholesterol of 5.5 mmol/l has a non-adherence risk score of 11 points, indicating a non-adherence risk of 50% (figure 1). These predictors of non-adherence are in accordance with other studies, who also reported that age and the absence of physical symptoms were predictors of non-adherence, suggesting that these patients do not realize the need for therapy [31]. By using this prediction model time consuming interventions like motivational interviewing can be limited to those who are at high risk of being non-adherent.

In the current study, non-adherence was reported in only 11% of the study population. This is much lower than in previous meta-analysis on statin non-adherence. Naderi et al. reported an adherence percentage of approximately 57% in 4 primary prevention studies with statins [14]. Lemstra et al. described similar results in 24 cohort studies. However, a much higher percentage of adherence was observed in the 3 RCTs. They reported percentages of adherence of 90% [17]. These differences can be explained by more frequent follow-up visits with more lipid testing, observations and more intensive follow-up of non-adherence. Our follow-up consists of 1 or 2 visits yearly, resulting in a similar good adherence as in these latter more intensive studies. Hollman et al., did not show a significant correlation between adherence and knowledge about the disease. This might be different in our population, because we explain FH to the individual patient, the families and colleges for patients. Moreover, they receive an explanation about the effect of treatment on their lipid profile during each consulta-

tion to increase awareness [35]. Motivation and behavioral changes starts with awareness of risk behavior, disease knowledge alone is probably insufficient to achieve changes [36]. The good adherence in our study may be based on the systematic feedback of treatment results.

It should be noted that the percentage side effects (27%) in our study is much higher than the incidence of adverse effects of statins in RCT's [37]. They reported a prevalence of 1-5%, while observational studies demonstrate side effects in 10%. This shows that side effect are rarely a reason for being non-adherent in our motivated population.

Our study has a number of strengths and limitations. The developed model based on age, untreated and treated total cholesterol is easily to use during patient consultation. It should, however, be noted that self-reported questionnaires are known to collect social desirable answers and overestimate adherence compared to objectively measured adherence with for instance the Medication Electronic Monitoring System (MEMS) [38, 39]. However, our patients, who reported non-adherence, clearly had higher LDL-C levels. Our model is developed in a single centre FH population with a limited number of patients, and it therefore needs validation in a larger population. Another potential limitation is that possible confounding by the care provider cannot be excluded in an open observational designed study.

In conclusion, a prediction model is developed with good discriminative capabilities to identify non-adherent FH patients. Only a low percentage of non-adherence was reported in our population, despite frequent side effects. Our model might aid in improving statin adherence in this extremely high risk group, which could potentially further prevent cardiovascular disease. This prediction model in combination with appropriate actions needs to be tested in future prospective research.

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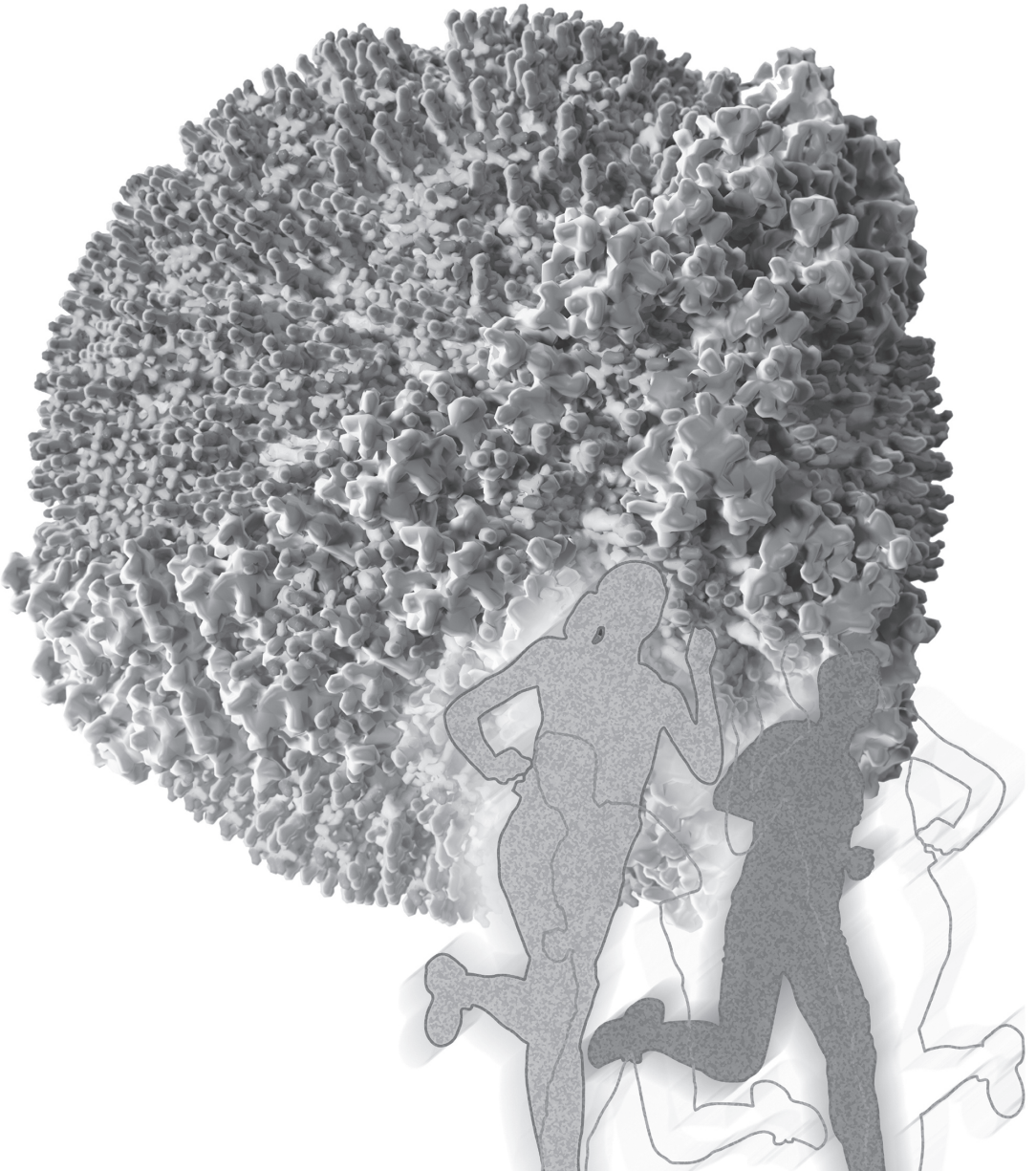

Chapter 6

Management of familial hypercholesterolemia: do women differ from men?

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Submitted

Abstract

Background

Evidence regarding management of women with familial hypercholesterolemia (FH) remains limited.

Objective

We examined lipid profile, lipid-lowering therapy, side effects of statins, treatment effectiveness and its associated factors in women with FH and compared the parameters with those from men.

Methods

Study population includes adult patients with FH (n=363) treated at our lipid clinic between 2008-2010. Multivariable linear regression analysis was applied to determine the variables associated with effectiveness of lipid-lowering treatment, defined as a continuous outcome of percentage reduction in total cholesterol (TC) levels in response to treatment.

Results

Women had higher TC levels at baseline compared to men (10.3±2.7 mmol/L vs. 9.7±1.9 mmol/L P=0.02). 64.5% of women, compared to 75.7% of men, received maximum statin therapy (P=0.02). Nevertheless, mean percentage reduction in TC level was 43.9%±15.4% in women and 46.7%±14.0% in men (P=0.08). In multivariable-adjusted models, reduction in TC levels among women was associated positively with age (Beta; 95% confidence interval: 0.2;0.1,0.4), treatment with atorvastatin (6.6;1.6,11.7) and rosuvastatin (6.4;0.4,12.3), maximum statin therapy (6.6;2.0,11.2); and inversely with presence of side effects (-5.4;-9.9,-0.9). Among men, it showed a positive association with lipid-lowering diet (8.3; 1.8,14.7), addition of ezetimibe to atorvastatin (6.9;2.8,11.1) and to rosuvastatin (9.1;2.7,15.5); and inverse associations with smoking (-5.9;-10.9,-0.9) and alcohol (-6.6;-11.2,-2.0).

Conclusions

Our findings underscore the lower likelihood for women to receive maximum therapy, despite their poorer lipid profile, and emphasize the impact of statin side effects on achieving the desirable clinical outcomes among women.

Introduction

Familial hypercholesterolemia (FH) is the most common genetic disorder leading to severely elevated serum cholesterol levels [1]. Genetic defects in FH arise from mutations affecting the low-density lipoprotein receptor (LDLR), Apolipoprotein B (APOB), proprotein convertase subtilisin kexin type 9 (PCSK9) or, in rare cases, the autosomal recessive hypercholesterolaemia (ARH) adaptor protein [2].

FH is associated with an increased risk of premature atherosclerosis. The risk of coronary artery disease (CAD) in FH patients has been estimated as >30% in women by age 60 and >50% in men by 50 years of age [3]. Intensive lipid management is therefore necessary to prevent cardiovascular disease (CVD) [3-6]. Statins constitute the first line treatment for patients with FH [7]. Despite improvements in lipid-lowering therapy in the last few years, most FH patients do not achieve optimal therapeutic lipid levels and residual risk of CVD is still present [8, 9].

Women with FH comprise a high-risk group which remains under-investigated [10]. In other high-risk populations, such as diabetics, women seem to receive less lipid-lowering therapy and have experienced poorer lipid control compared men [11, 12]. While higher incidence of statin adverse effects in women have been suggested, evidence regarding gender-related statin adverse effects remains controversial [13-17]. Based on longitudinal studies, little is known about management of FH women compared to their male counterparts [18, 19]. It is therefore essential to investigate potential gender differences in management of FH patients and the factors contributing to the effectiveness of treatment interventions among women and men.

In a well-defined cohort of FH patients, we aimed to study the differences between women and men in lipid profile, lipid lowering therapy, and side effects of statins. Further, we assessed the factors associated with treatment effectiveness among women and men with FH.

Methods

Study population and design

Our specialized university centre lipid clinic treats patients with cardiovascular diseases and inherited lipid disorders, mainly FH. All consecutive adult patients with heterozygous FH who visited our out-patient clinic between 1 January 2008 and 31 December 2009 were considered eligible for inclusion in this study. Diagnosis of FH was based on either identification of a FH causing mutation in the LDLR, APOB or PCSK9 gene or on the following clinical criteria: LDL cholesterol level >the 95th for age and gender specific percentile in combination with at least one of the followings: presence of xanthomas, LDL-cholesterol level

>95th percentile for age and sex in a first degree relative, or premature coronary heart disease (CHD) (defined as male <55y, female <60y) in a first degree relative using the criteria of Aalst-Cohen [20]. All consecutive adult patients with heterozygous FH were considered eligible for inclusion in this study. From 398 patients, we excluded FH patients with normal LDL cholesterol levels at baseline (N=7), were not on lipid lowering therapy (N=8), were only on ezetimibe monotherapy (N=2), and FH patients who were pregnant (N=18). In total, 363 FH patients (186 women and 177 men) were included in the current study.

In 79% of the FH patients, a pathogenic mutation was identified. All patients included in the study provided written informed consent and completed a baseline questionnaire. The response rate for the questionnaire was 100% and there was no missing information. The questionnaire was developed in cooperation with experts from the Cardio Vascular Genetic (CVG) team. Patients were asked about the highest total cholesterol level ever registered. Additionally, they provided information regarding the date of initiating lipid lowering therapy as well as the type of medications and the doses used. Subsequently, questions related to side effects, as multiple choice of different types of side effects related to the treatment use, were asked. Based on the number of reported side effects, we made 3 categories of one, two, and three or more side effects. The influence of side effects on quality of life was assessed using health status questionnaire and graded on a scale comprising from none, some, or severe.

Questions about adherence of medication, family history of premature CHD, history of CVD, quality of life, as well as characteristics such as education and lifestyle parameters including physical activity and risk factors such as smoking and alcohol consumption were provided. High education was defined as type of education (college or university). Alcohol consumption was defined as type of alcohol (liquor, beer and wine) and amount of alcohol consumed per week. Physical activity was defined as any type of exercise (walking, cycling, gardening, sporting or other exercises) 30 minutes per day.

All information provided in the questionnaires was revalidated with the medical records. Patient characteristics, including age, sex, body mass index, laboratory values and blood pressure were abstracted from medical records.

All patients were carefully monitored annually at the lipid clinic by a specialized vascular nurse. They received regular patient tailored education about their disease, lifestyle advices, benefits of using statins and the effect of treatment on lipid profiles. Patients were asked in every visit how many times they deviated from the regime according to the European guideline for the management of

dyslipidaemias [4]. Side effects were discussed and statins were changed when necessary. Prescribing medication was reserved to the physician.
During consultation, patients were physically examined to obtain the measures of height, weight, and blood pressure. A fasting lipid blood sample was taken. Hypertension was defined as blood pressure >140/>90 mmHg on more than 2 occasions or the use of a prescribed antihypertensive medication. Type II diabetes mellitus was diagnosed according to the World Health Organization (WHO) criteria or the use of prescribed anti-diabetic medication [21]. CVD was defined as myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or ischemic cerebrovascular accident. The majority of the patients (80%) completed the questionnaire directly after their visit. Patients, who forgot to send back the questionnaire, were called by the specialized nurse. Unanswered questions were completed during the following visit.

Lipid-lowering therapy
Lipid-lowering drugs were identified and classified at the level of the therapeutic class (ie, statins, bile acid sequestrants, fibric acid derivatives, nicotinic acid derivatives, or other lipid-lowering drugs).
Three main categories of statins (atorvastatin, rosuvastatin, simvastatin) were created to include statins which were mostly used in the cohort.

Treatment effectiveness
The treatment effectiveness included as the outcome measure in the current study was reduction in total cholesterol (TC) levels after treatment with statins. This was defined as: (1) percentage of TC reduction from baseline [decrease in TC level (%) = (untreated TC – treated TC) / untreated TC]. This variable was used as a continuous outcome; (2) ≥50% reduction in TC levels; a dichotomous outcome variable with values of yes or no. Low-density lipoprotein (LDL) cholesterol reduction to <2.6 mmol/l was not used as an outcome measures as it comprised a very small group of patients in our cohort (N=35, 18.6% of women; N=32, 18.1% of men). Our choice of the outcome measure was oriented towards a clinically meaningful concept for both clinical practitioners and patients and relates to the 2007 European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) guidelines [4] as they were used at the time our study was established.

Statistical analyses

Descriptive statistics were performed to provide the full picture of baseline characteristics. The values were presented as mean±Standard Deviation (S.D.) for continuous variables and numbers (percentages) for dichotomous variables. Chi-square tests were performed to assess differences in proportions and the student t-test was used to assess differences in means.

All the analyses were performed separately for women and men. We developed multivariate linear regression models which included the variables that were significantly associated with the continuous outcome in univariate analyses as well as a priori defined predictors and confounders namely age, history of CVD, family history of premature CHD, type of statins, maximum statin dose therapy, and statin side effects. Different statins were included in the model as dummy variables for atorvastatin, rosuvastatin, and simvastatin with simvastatin as the reference category. We checked for possible nonlinearity in the association of the variables with the outcome and for effect modification between age with treatment effectiveness and with side effects by adding quadratic and interaction terms respectively. Inclusion of the variables for the final model was determined by backward stepwise elimination of the least significant variables until all variables in the model had a p-value ≤0.1. The analyses were performed using SPSS software version 23 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and R (3.2.3). Statistical significance was defined as P ≤0.05.

Results

General characteristics

Table 1 details the demographic characteristics of 363 FH patients (186 women and 177 men) included in the study. Women consumed less alcohol and adhered more frequently to a lipid lowering diet. Family history of premature CHD was more prevalent among women. Women had higher levels of both untreated and treated TC as well as treated LDL and high density lipoprotein (HDL) cholesterol and lower levels of treated triglycerides.

Lipid-Lowering Therapy

Of the patients using statins, the majority used atorvastatin (40.3% in women and 50.8% in men, P=0.04), followed by rosuvastatin (with 23.1% in women and 18.6% among men) and simvastatin (with 33.3% in women and 28.2% among men) (table 2).

Smaller proportion of women (64.5% in women and 75.7% in men, P=0.02) were on maximum dose statin therapy; defined as 40 mg rosuvastatin, >40 mg ator-

Table 1. Characteristics of FH patients, according to gender

	Women n=186	Men n=177	p [a]
Age (years), mean ±SD	45.9±14.7	45±12.7	0.51
BMI (kg/m^2), mean ±SD	26.2±4.8	26.2±3.7	0.99
Current smokers, n (%)	29 (15.6)	30 (16.9)	0.73
Alcohol consumption, n (%)	108 (58.1)	142 (80.2)	**<0.01**
Lipid lowering diet, n (%)	180 (96.8)	161 (91.0)	**0.02**
Physical activity, n (%)	135 (72.6)	114 (64.4)	0.09
Hypertension, n (%)	32 (17.2)	28 (15.8)	0.72
Diabetes, n (%)	7 (3.8)	6 (3.4)	0.90
Hyper-hypothyroidism, n (%)	8 (4.3)	3 (1.7)	0.15
History of CVD [b], n (%)	25 (13.4)	22 (12.4)	0.77
Family history of premature CHD [c], n (%)	138 (74.2)	113 (63.8)	**0.03**
High education, n (%)	101 (54.3)	114 (64.4)	0.50
FH signs, n (%)	60 (32.3)	57 (32.2)	0.99
DNA mutation, n (%)	144 (77.4)	142 (80.2)	0.51
Untreated total cholesterol, mmol/L	10.3±2.7	9.7±1.9	**0.02**
Treated lipid profiles, mmol/L			
Total cholesterol, mean ±SD	5.5±1.5	5.0±1.1	**<0.01**
LDL cholesterol, mean ±SD	3.5±1.4	3.3±1.0	0.08
HDL cholesterol mean ±SD	1.5±0.4	1.2±0.3	**<0.01**
Triglyceride, mean ±SD	1.1±0.5	1.2±0.7	**0.03**

BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number; SD, standard deviation.

[a] *P-value for the difference between women and men.*

[b] *CVD is defined as myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or ischaemic cerebrovascular accident.*

[c] *Premature CHD is defined as a CHD event before the age of 55 (in men) or 60 (in women).*

vastatin, 80 mg simvastatin. There were no gender differences in the adherence to treatment as well as in the duration of statin use **(table 2)**.

Tolerability

Overall, side effects attributed to lipid-lowering therapy were reported by 57.2% of women and 42.8% of men. The prevalence of patients reporting three or more side effects was higher in women (24.8%) compared to men (19.7%), albeit not statistically significant **(table 2)**. Myalgia was the most common reported

Table 2. Treatment characteristics for FH patients, according to gender

	Women n=186	Men n=177	p [a]
Lipid lowering treatment	75 (40.3)	90 (50.8)	**0.04**
Atorvastatin, n (%)	43 (23.1)	33 (18.6)	0.30
Rosuvastatin, n (%)	62 (33.3)	50 (28.2)	0.08
Simvastatin, n (%)	6 (3.2)	4 (2.3)	0.90
Other statins [b], n (%)	164 (88.2)	158 (89.3)	0.74
Adherence to medication >90%, n (%)	8.5±6.0	9.4±6.0	0.16
Statin use (years), mean±SD	120 (64.5)	134 (75.7)	**0.02**
High-intensity therapy [c], n (%)			
Treatment effectiveness			
Decrease in untreated TC (%), mean±SD	43.9±15.4	46.7±14.0	0.08
≥50% decrease in total cholesterol, n (%)	75 (39.9)	87 (49.2)	0.07
LDL<2.6 mmol/l, n (%)	35 (18.8)	32 (18.1)	0.90
Side effects			
Side effects, n (%)			0.38
no side effects	83 (44.6)	89 (50.3)	0.28
one side effect	30 (16.1)	29 (16.4)	0.98
two side effects	27 (14.5)	24 (13.5)	0.80
three or more side effects	46 (24.8)	35 (19.7)	0.26
ALT (U/L), mean±SD	27±18.7	41±21.8	**<0.01**
AST (U/L), mean±SD	26.5±9.6	31.2±10.4	**<0.01**
Creatine kinase (U/L), mean±SD	115.3±87.1	150.8±85.5	**<0.01**
Effect of statin therapy on Quality of life, n (%)			0.09
none	126 (67.7)	131 (74.0)	0.19
some	37 (19.9)	34 (19.2)	0.87
severe	23 (12.4)	12 (6.8)	0.07

LDL, low-density lipoprotein; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; FH, familial hypercholesterolemia, n, number; SD, standard deviation.

[a] P-value for the difference between women and men.

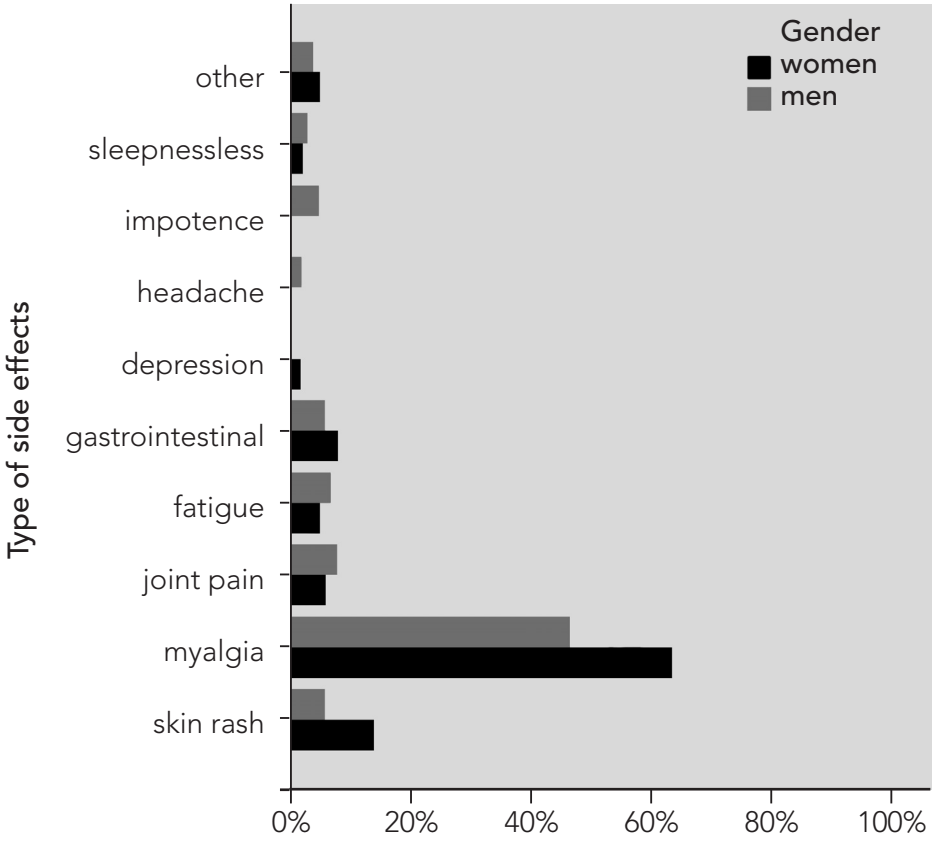
[b] other statins is included pravastatin and fluvastatin.

[c] High-intensity therapy is defined as Atorvastatin (>40 mg), Simvastatin (>40, 80 mg), Rosuvastatin (40 mg).

side effect among all side effects (reported by 60.2% of women and 53.4% of men) (**figure 1**). No major side effects such as rhabdomyolysis or >3 times upper limit of normal elevation of liver enzymes were reported. Women, compared to men, reported twice as higher severe impact of statin therapy on their quality

Figure 1. Types of statin side effects among FH patients on lipid lowering therapy, by gender.

Some patients reported more than one side effect



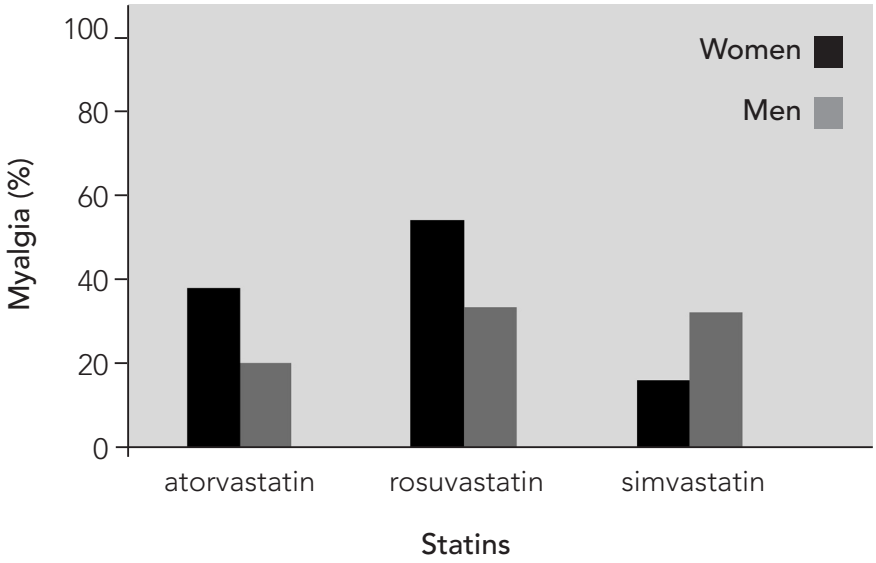
of life due to side effects (12.4% vs 6.8%, P=0.07). (table 2)

Figure 2 demonstrates the prevalence of the most common reported side effect (myalgia) for the three most used statins (atorvastatin, rosuvastatin, and simva statin) among women and men. While myalgia was reported by 53.5% of women and 33.3% of men receiving rosuvastatin, 37,3% of women and 20.0% of men on atorvastatin, and 16.1% of women and 32,0% of men on atorvastatin treatment reported this side effect.

Reduction in TC levels

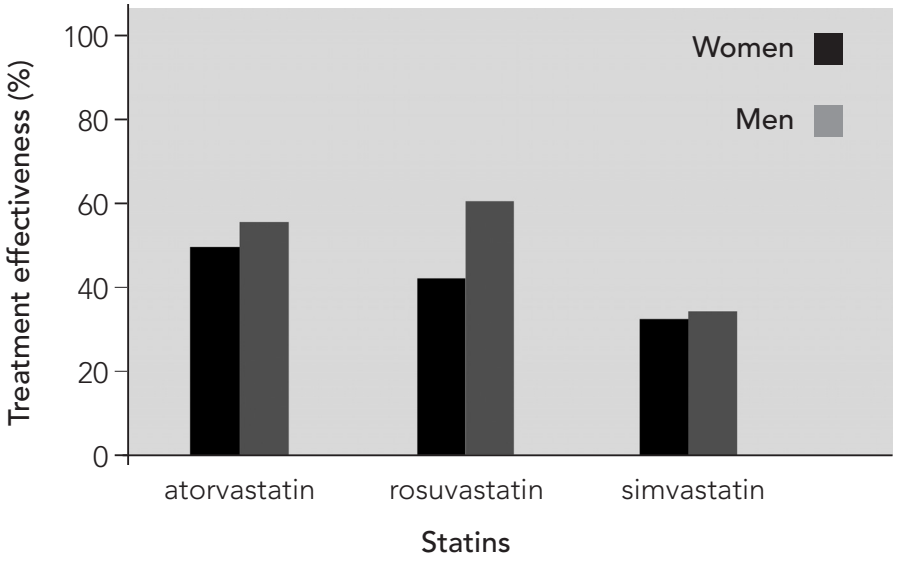
The mean percentage decrease in TC level was 43.9% in women and 46.7% in men (P=0.08). Overall, 39.9% of women and 49.2% of men reached ≥50% re-

Figure 2. Prevalence of myalgia for different statins by gender



** Prevalence of myalgia as the most common reported side effect for three different statins (atorvastatin, rosuvastatin, simvastatin) among women and men.*

Figure 3. Treatment effectiveness for different statins by gender



** Treatment effectiveness (reduction in untreated total cholesterol levels ≥50% for three different statins (atorvastatin, rosuvastatin, simvastatin) among women and men.*

Table 3. Associations between determinants and cardiovascular events

	Women (n=180) [a] B (95%CI)	p	Men (n=173) [a] B (95%CI)	p
Age	0.21 (0.06; 0.36)	0.01	0.35 (0.20; 0.51)	**<0.01**
BMI	-0.03 (-0.49; 0.43)	0.89	0.12 (-0.44; 0.68)	0.66
Smoking	-3.56 (-9.59; 2.47)	0.25	-7.01 (-12.49;-1.53)	**0.01**
Alcohol consumption	-1.97 (-6.46; 2.53)	0.39	-6.12 (-11.28;-0.96)	**0.02**
Lipid lowering diet	-0.53 (-12.92; 11.86)	0.93	13.18 (6.26; 20.01)	**<0.01**
Physical activity	1.99 (-2.94; 6.92)	0.43	0.98 (-3.38; 5.34)	0.66
Hypertension	6.52 (0.78; 12.25)	0.03	4.71 (-0.99; 10.41)	0.11
Diabetes	-2.63 (-14.13; 8.87)	0.65	9.36 (-1.95; 20.66)	0.10
History of CVD [b]	4.61 (-1.90; 11.12)	0.16	7.18 (1.01; 13.34)	**0.02**
Family history of premature CHD [c]	5.68 (0.68; 10.67)	0.03	5.44 (1.19; 9.69)	**0.01**
High-intensity therapyd	5.50 (0.85; 10.15)	0.02	3.82 (-1.13; 8.78)	0.13
Side effects	-3.90 (-8.32; 0.53)	0.08	-0.47 (-4.64; 3.70)	0.82

Beta coefficient (95% confidence interval) shows the crude (unadjusted) association between each patient's characteristic and treatment effectiveness (defined as a continuous outcome of percentage reduction in total cholesterol levels).

BMI; Body Mass Index; CHD; coronary heart disease; CVD; cardiovascular disease; FH; familial hypercholesterolemia; n; number.

[a] 10 FH patients (6 women and 4 men) receiving other statins (pravastatin or fluvastatin) were excluded from this analysis as we made 3 main categories to include statins which were mostly used in our cohort (atorvastatin, rosuvastatin, and simvastatin).

[b] CVD is defined as myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or ischaemic cerebrovascular accident.

[c] Premature CHD is defined as a CHD event before the age of 55 (in men) or 60 (in women).

duction in TC levels (P=0.07). Reduction in LDL cholesterol <2.6 mmol/l was achieved by only 18.6% of women and 18.1% of men. There were no gender differences in the adherence to treatment as well as in the duration of statin use (table 2). The untreated TC levels reduced in 49.3% of women receiving atorvastatin and 60.6% of men receiving rosuvastatin whereas simvastatin was the least potent statin in reducing TC levels (figure 3).

Results of the univariate linear regression analysis for the association between reduction in TC levels (a continuous outcome defined as percentage decrease in TC) with different patient characteristics for women and men are shown in Supplemental table 1. The results of the ordinary least squares regression model predicting percentage change in TC levels from baseline are shown in table 3.

Among women, the variables (Beta; 95% confidence interval) positively associated with the outcome were age (0.22;0.07,0.37), treatment with atorvastatin (6.64;1.58,11.70), with rosuvastatin (6.38;0.45,12.31), and maximum dose statin regimen (6.62;2.02,11.21). Presence of side effects (-5.37;-9.85,-0.89) was inversely associated with the outcome among women. Among men, adherence to the lipid lowering diet (8.28; 1.83,14.72) and addition of ezetimibe to atorvastatin (6.95;2.80,11.11) and to rosuvastatin (9.08;2.66,15.49) were positively associated with the outcome and smoking (-5.88;-10.90,-0.86), alcohol consumption (-6.61;-11.23,-1.99) showed to be inversely associated with the outcome.

Discussion

In the current study, we report differences between women and men in lipid profile, lipid lowering therapy, statin adverse effects, and factors associated with treatment effectiveness in a well-defined cohort of FH patients. Despite higher TC levels at baseline, women were less likely to receive maximum therapy. Nevertheless, treatment effectiveness was not significantly lower for women compared to men. Women were more likely to experience three or more side effects due to statins and a larger proportion of them reported severe impact of statin therapy on their quality of life. Importantly, presence of side effects was inversely associated with treatment effectiveness among women. On the other hand, behavioral factors such as smoking, alcohol consumption, and adherence to lipid lowering diet were associated with treatment effectiveness in men.

In contrast with some studies, [22, 23] we observed higher TC levels for women at baseline in our study. Nevertheless, women appeared to be less likely to receive maximum dose statin treatment. This finding is in line with the report from the SAFEHEART study that found female sex to be independently associated with less likelihood of the use of high-intensity statins [19]. Due to the paucity of data with regard to gender differences in treatment with statins, the effectiveness and benefits of statin therapy for primary CVD prevention among women in the general population has been controversial [24-27]. To overcome the gender bias in the management of women, a secondary analyses of the PROVE IT-TIMI 22 trial provided robust evidence regarding the safety, efficacy, and the clinical impact of intensive statin therapy to reduce the CVD events among women [28]. These results, in line with other trials regarding the efficacy of intensive statin treatment in CVD prevention among high risk women, [29] reinforces the value of intensive statin therapy among women with FH. Despite lower proportion of women receiving maximum therapy in our study, treatment effectiveness was

not significantly lower for women compared to men which could suggest that women have a more robust TC reduction on lower statin doses compared to men.

Extensive clinical evidence supports the efficacy, safety, and tolerability of statin treatment for prevention of CVD [7, 13]. However, there is a paucity of information in the area of statin-related adverse effects in adult FH patients. A previous study on predicting non-adherence in patients with FH, has cited 27% side effects [8]. Another study reported only a total of 55 FH patients, out of 781, to have discontinued medication. However, 45% of this withdrawal was due to statin adverse events [30]. The most commonly reported side effect of statins was myalgia. While several meta-analyses of randomized clinical trials comparing statins to placebo have shown increased myalgia in patients receiving statins, the evidence regarding myalgia is rather mixed [31]. In our study, side effects, mainly myalgia, were reported by a large proportion of patients; 33.9% of women and 26.0% of men. While there was no gender difference in the overall percentage of patients who reported any side effect, women were more likely to report having experienced three or more side effects. Women and men on simvastatin treatment reported the smallest proportion of myalgia, while the largest proportion was among rosuvastatin users in both genders. Compared to men, a larger proportion of women in our study reported a severe effect on their quality of life associated with lipid-lowering medications. Importantly, while serious or fatal statin adverse events are rare, common side effects such as myalgia might affect the adherence to treatment in long-term.

International guidelines consider FH patients to be at high risk for CVD [3-6, 32]. To prevent CVD, intensive lipid management in women and men with FH is therefore of paramount importance. According to the previous studies and 2007 ESC/EAS guidelines, treatment recommendations included the use of high potency statins titrated to optimally achieve 50% reduction in total and LDL cholesterol levels or treated TC of <5.0 mmol/l and treated LDL cholesterol level of <2.6 mmol/l [4]. Although the use of maximum treatment regimen has been considered effective for attaining these treatment levels [33] only around 18% of women and men in our FH cohort reached LDL cholesterol levels <2.6 mmol/l and approximately half of the patients achieved the 50% reduction in baseline TC levels. The small percentage of FH patients attaining the LDL treatment goal in our study is in line with the report from a cross-sectional study of FH patients in the Netherlands [9]. Nevertheless, the high adherence rates of our FH patients (87.2% of women and 89.3% of men) can be a reflection of patients' self-management and the availability of a dedicated FH care in our clinic.

Thus far, gender-related differences in the effectiveness of lipid lowering therapy and its associated factors have not been adequately clarified. Only few studies have compared the effects between women and men and none have assessed gender differences among FH patients. In our cohort of FH patients, we showed gender differences in the effectiveness of different types of statins. Among the three main categories of statin in our study, atorvastatin and rosuvastatin were significantly associated with treatment effectiveness in women while addition of ezetimibe to the statin treatment led to the treatment effectiveness in men. Importantly, statin side effects were inversely associated with achieving the desirable clinical outcomes in women. This highlights the need to investigate gender related differences in the role of pharmacokinetics and pharmacodynamics, as well as the impact of pharmacogenetics on both. Behavioral factors such as smoking, alcohol consumption, and adherence to lipid lowering diet were inversely associated with treatment effectiveness in men but not in women. These results underscore the need for promotion of healthy lifestyle through counseling programs to further emphasize the central role of lifestyle as the foundation to benefit from cholesterol-lowering therapy.

The results of our study must be considered within the context of its strengths and limitations. To our knowledge, our study is the first to investigate gender differences in lipid profile, lipid lowering therapy, statin side effects, as well as treatment effectiveness and its associated factors in FH patients. We had access to a well-defined cohort of FH patients with detailed information regarding patients' characteristics, treatment regimens, and side effects. Our unique database is based on data obtained from clinical practice and questionnaires. However, it represents a single center with a limited number of patients and our results, therefore, need to be validated in other FH patient populations.

Conclusion

We reported gender differences in lipid profile, lipid lowering therapy, statin adverse effects, and factors associated with treatment effectiveness in a well-defined cohort of patients with FH. Our study highlights the lower likelihood for women to receive high-intensity therapy despite their poorer baseline lipid profile and emphasizes the negative impact of statin side effects on achieving the desirable clinical outcomes among women.

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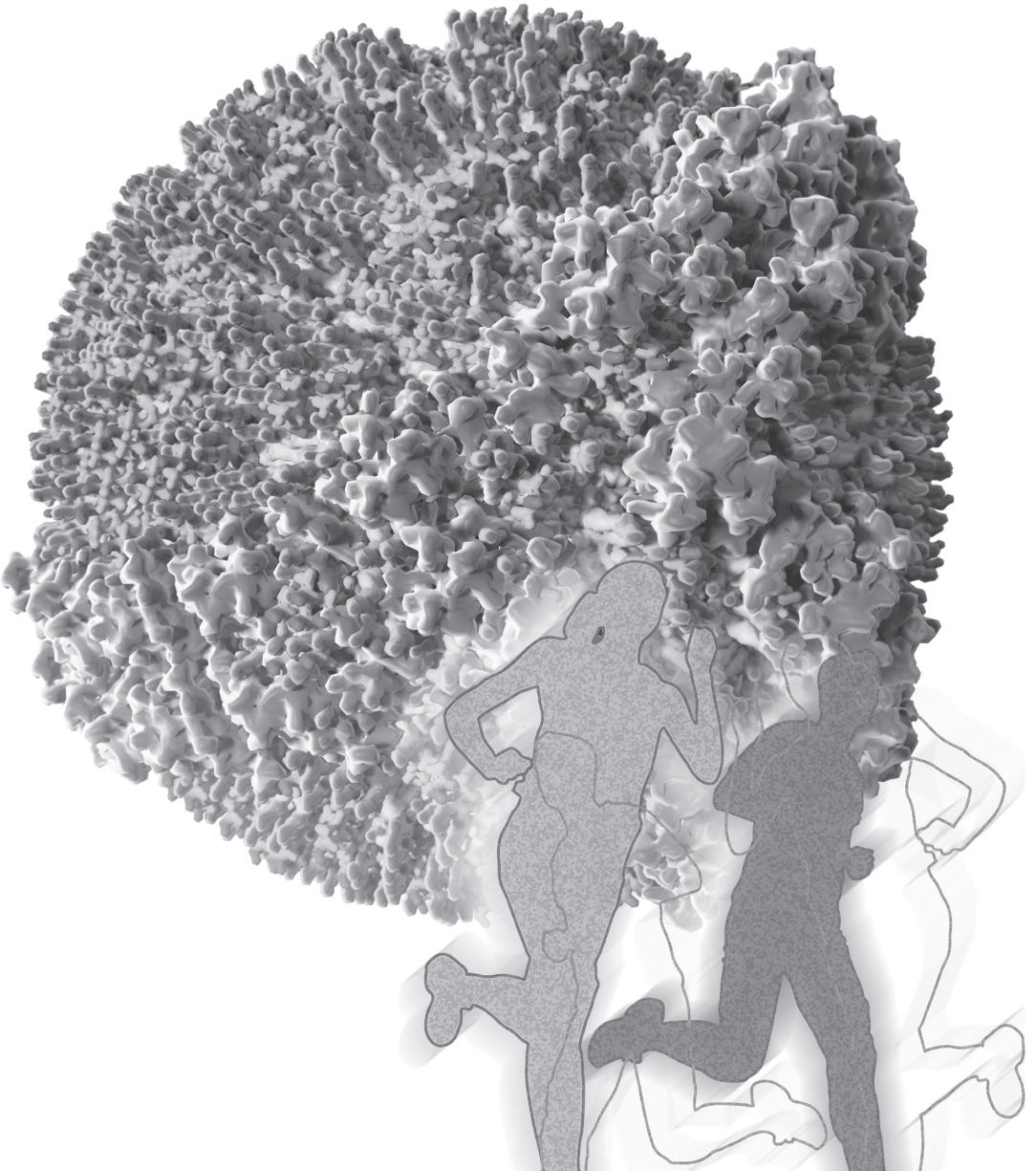

Chapter 7

Proprotein convertase subtilisin/ Kexin 9 inhibition in patients with familial hypercholesterolemia: initial clinical experience

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Abstract

Background

Despite optimal lipid-lowering therapy, a minority of patients with familial hypercholesterolemia (FH) reach LDL-cholesterol (LDL-C) target goals. In randomized trials Proprotein convertase subtilisin/Kexin 9 (PCSK9) inhibitors led to impressive LDL-C reductions and a favorable safety profile. However, data about the efficacy and safety outside clinical trials is not available yet.

Objective

To describe efficacy and side effects of PCSK9 inhibitors in FH patients in clinical practice.

Methods

Registry of all consecutive FH patients who started with a PCSK9 inhibitor at a lipid clinic of a university hospital.

Results: We analyzed 83 FH patients (79 heterozygous FH (heFH) (65 with a genetically confirmed heFH, 14 with clinical heFH and 4 homozygous FH (hoFH)), with a mean age of 55.1±11.6 years. Treatment with a PCSK9 inhibitor resulted in an additional reduction of 55%±21% in mean LDL-C levels. Patients with heFH had more LDL-C decrease than patients with hoFH (56% vs 38%). Patients using ezetimibe monotherapy because of statin-intolerance (n=24, 29%) had less LDL-C decrease compared to patients who concurrently used statin therapy (47% and 58%, p=0.03).

Side effects of PCSK9 inhibitors were reported by 32 patients (39%). Flu-like symptoms (n=12) and injection site reactions (n=11) were most frequent. Seven patients (8%) discontinued treatment, five because of side effects, two because of non-response.

Conclusion

Our initial experience of PCSK9 inhibition in FH patients in a clinical setting showed comparable reduction in LDL-C levels but more side effects compared to clinical trials.

Introduction

Familial hypercholesterolemia (FH) is the most common autosomal dominant disorder of the lipid metabolism, mainly caused by gene mutations in the low density lipoprotein receptor (LDLR) [1]. Based on an estimated prevalence of 1:244 persons, the expected number of FH patients in the Netherlands is 70.000 [2]. FH is characterized by elevated plasma levels of LDL-Cholesterol (LDL-C) and is associated with an increased risk of premature cardiovascular disease (CVD) [3, 4]. However, timely initiation of lipid lowering therapy (LLT) in combination with lifestyle modification is very effective for CVD prevention in these patients [5-7]. Last decades more potent statins have been developed and the addition of ezetimibe to LLT resulted in further improved cardiovascular outcomes [8, 9]. However, only a minority of FH patients reaches LDL-C treatment goals even with maximum LLT [10-12].

Recently a new class of lipid-lowering therapy, Proprotein Convertase Subtilisin / Kexin 9 (PCSK9) inhibitors, has been developed for those high risk patients not reaching LDL-C target despite maximum tolerated LLT. Currently two PCSK9 inhibitors are available: evolocumab and alirocumab. In randomized controlled trials, these monoclonal antibodies show a LDL-C reduction up to 60%. In general, PCSK9 inhibitors are well tolerated in these trials with most common adverse events reported by ≥5% in patients treated with alirocumab or evolocumab, occurring more frequently than with placebo [13-16]. However, it is important to ensure that data from clinical trials apply to real-life settings as well, especially when it concerns long term safety. This will improve the applicability of the trial evidence to daily practice.

The goal of our study was to evaluate our initial clinical experience regarding efficacy and side effects of PCSK9 inhibitors in FH patients outside clinical trials.

Patients and methods

Participants

Patients with FH were recruited from the out-patient clinic specialized in (inherited) lipid disorders of Erasmus MC. The diagnosis heterozygous FH (heFH) was based on either the identification of an FH causing pathogenic mutation in the LDLR, APOB or PCSK9 gene or in those without an FH mutation (genetic heFH), a clinical diagnosis of FH was made by a Dutch Lipid Clinic Network score of ≥6 representative of probable or definite FH (clinical heFH) [17, 18]. Homozygous FH (hoFH) was defined as either true homozygous FH (two similar LDLR or APOB mutations), compound heterozygous FH with two different LDLR or two different APOB mutations, or double heterozygous as one LDLR and one APOB mutation.

The following patients with confirmed FH ≥18 years were considered eligible for treatment with PCSK9 inhibitors in our institute because of very high risk of CVD defined as:

1. HeFH patients without CVD events, on maximum tolerated statin and ezetimibe therapy with LDL-C >3.5 mmol/L (135 mg/dL).
2. HeFH patients with CVD events, on maximum tolerated statin and ezetimibe therapy with LDL-C >2.5 mmol/L (100 mg/dL).
3. HoFH patients who did not carry two LDLR negative mutations on maximum tolerated statin and ezetimibe therapy, with LDL-C >3.5 mmol/L (135 mg/dL) without CVD events or LDL-C >2.5 mmol/L (100 mg/dL) with history of CVD events.
4. FH patients with documented statin intolerance defined as statin-associated myalgia for at least three different statins in accordance with the flow chart described by EAS/ESC consensus and in combination with ezetimibe monotherapy with LDL-C >3.5 mmol/L (135 mg/dL) without CVD events or LDL-C>2.5 mmol/L (100 mg/dL) with history of CVD events [19].

All patients fulfilled the Dutch criteria for reimbursement of PCSK9 inhibitors. In case of FH these criteria are having an LDL-C >2.5 mmol/L (100 mg/dL) without CVD events or an LDL-C >1.8 mmol/L (70 mg/dL) with a history of CVD events, despite optimal statin treatment and ezetimibe [20].

Patients started with a PCSK9 inhibitor (evolocumab 140 mg subcutaneously every two weeks (heFH patients) or 420 mg subcutaneously every two weeks (hoFH patients) or alirocumab 75 mg or 150 mg subcutaneously every two weeks (heFH patients)) between 1 May 2016 and 14 October 2016 as part of clinical care. There was no preference for either evolocumab or alirocumab. All patients had at least 2 PCSK9 inhibitor subcutaneous injections between baseline and on-treatment measurements.

According to the Medical Ethical Research Committee this study was not subject to the Medical Research involving Human Subjects Act. We only used data of patients, who provided written consent for research and anonymous publication of their clinical information.

Study design

All patients were treated at the outpatient lipid clinic by the cardiovascular genetic team consisting of a lipidologist, a nurse practitioner, a fellow vascular medicine and two nurses specialized in family counselling according to the European guideline for the management of dyslipidaemias [21].

The follow-up started at the date patients received instructions of how to use

the auto-injector and administrated the first injection PCSK9 inhibitor subcutaneously. The effects on lipoprotein profile, side effects and adherence were monitored. Blood (lipoproteins, glucose and liver tests) was measured before and after 6 weeks when patients had an regular appointment at the out-patient clinic. Side effects, injection-site reactions and adherence of lipid lowering therapy was systematically discussed during each consultation.

Clinical data such as LDLR, APOB and or PCSK9 gene mutations, plasma lipoprotein levels (total cholesterol, triglycerides, LDL-C, apolipoprotein B and HDL-cholesterol), liver tests (ASAT, ALAT, gamma-glutamyl-transferase), current and previous LLT, CVD events, adherence, side effects, injection site reactions and general characteristics (age, sex and body mass index (BMI)) were collected from the patients' files and entered in a database.

High-intensity statin was defined as atorvastatin (40-80mg), rosuvastatin (20-40mg) or simvastatin 80mg with ezetimibe. Moderate intensity statin was defined as atorvastatin (10 to <40mg), rosuvastatin (5 to <20mg) or simvastatin (20-40mg), pravastatin (40mg), fluvastatin (40-80mg) and low intensity as atorvastatin (<10mg), rosuvastatin (<5mg), simvastatin (<20mg), pravastatin (<40mg) or fluvastatin (<40mg) [22].

Maximum tolerated LLT was defined as the maximum dose of statins to which patients could adhere without unbearable side effects in combination with ezetimibe. Statin intolerance was defined as documented unbearable side effects of at least three statins including low dose statins on non-daily basis [19].

Smoking was defined by start and stop dates from the patients file. Smoking cessation was defined as stopped >1 year. Overweight was defined as BMI>25 kg/m^2. Hypertension was defined as blood pressure >140/>90 mmHg on more than two occasions or the use antihypertensive medication [23]. Type 2 diabetes mellitus was diagnosed according to the American Diabetes Association or the use anti-diabetic medication [24]. CVD was defined as having been diagnosed with either myocardial infarction, angina pectoris confirmed by a cardiologist, coronary artery bypass grafting or percutaneous coronary intervention, transient ischemic accident or stroke diagnosed by a neurologist or a peripheral arterial disease diagnosed by vascular surgeon [25]. These events were collected from the patients' medical records.

Statistics

All data were analysed anonymously using SPSS Statistics for Windows, version 23.0 (IBM Corp.). Dichotomous variables are reported as numbers and percentages. Continuous variables are presented as mean±standard deviation (SD) or

median and interquartile range (IQR). The Shapiro-Wilks test was used to assess whether data were normally distributed. Differences between subgroups of FH patients were analysed by chi-square, Student's t-test and paired t-test as appropriate. For all tests a p-value less than 0.05 was considered statistically significant.

Results

A total of 83 FH patients (47% women, mean age 55.1±11.6 years) started either evolocumab (n=52) or alirocumab (n=31) in addition to maximal tolerated LLT. The baseline characteristics of the FH patients according to PCSK9 inhibitor are shown in table 1.

Fifty patients used evolocumab 140 mg subcutaneously every two weeks and two hoFH patients used evolocumab 420 mg every two weeks. Twenty-nine patients used alirocumab 150 mg subcutaneously every two weeks and two patients alirocumab 75 mg subcutaneously every two weeks. The majority (83%) of the FH patients were carrier of a pathogenic mutation in the LDLR (73%) or APOB (10%) gene. The diagnosis of heFH was genetically (78%) or clinically (17%), 5% had hoFH. Sixty percent of our patients had a history of CVD, mainly coronary artery disease (52%). Other cardiovascular risk factors were frequent: especially overweight (66%), hypertension (40%) and diabetes mellitus (13%). On the other hand only a minority (5%) were current smokers. Seventy-one percent of the patients used statins in combination with ezetimibe and half (49%) of the statin-users were treated with high-intensity statin therapy, 29% used ezetimibe monotherapy because of statin intolerance.

At baseline the mean total cholesterol level was 6.9±2.3 mmol/L (267±89 mg/dL) and LDL-C 5.0±2.1 mmol/L (193±81 mg/dL). HeFH patients had a mean LDL-C of 4.9±2.1 mmol/L (190±81 mg/dL) and hoFH patients had, as expected, a markedly higher mean LDL-C of 7.4±4.3 mmol/L (286±166 mg/dL). The mean time between baseline levels and those during PCSK9 inhibitor treatment was 41±48 days.

Efficacy

The addition of PCSK9 inhibitor therapy resulted in a mean LDL-C decrease of 55%±21% and a median LDL-C decrease of 58%, IQR 43%-72% in the total population; in heFH patients a mean LDL-C decrease of 56%±20% and a median LDL-C decrease of 58%, IQR 43%-72% and in hoFH patients a mean LDL-C decrease of 38%±32% and a median LDL-C decrease of 47%, IQR 5%-62% was observed.

Table 1. General characteristics of patients with FH before starting PCSK9 inhibitors at baseline

	Baseline n=83
Age (years) mean±SD	55.1±11.6
Women, n(%)	39 (47)
Caucasian, n(%)	76 (92)
History of CVD, n(%)	50 (60)
Cardiovascular risk factors, n(%)	
Ever smoker	39 (47)
Current smoker	4 (5)
BMI mean±SD	27.3±4.0
History of hypertension	33 (40)
DM type 2	11 (13)
FH	83 (100)
• Heterozygous	65 (78)
• Homozygous	4 (5)
• Clinical	14 (17)
Lipid lowering therapy, n(%)	
• Statin use	59 (71)
• High intensity	41 (49)
• Moderate intensity	14 (17)
• Low intensity	4 (5)
• Ezetimibe	83 (100)
• Ezetimibe monotherapy	24 (29)
Lipid values, mean±SD	
• Total cholesterol (mmol/l)*	6.9±2.3
• LDL cholesterol (mmol/l)*	5.0±2.1
• HDL cholesterol (mmol/l)*	1.4±0.6
• Triglyceride (mmol/l)†	1.7±1.2
• Apo B (g/L)	1.5±0.6
• Glucose (mmol/l)	5.8 ±1.3
Liver tests, mean±SD	
• ASAT (U/L)	27.5±9.1
• ALAT (U/L)	30.2±13.9
• Gamma GT (U/L)	32.2±19.4

LDL=low density lipoprotein; HDL= high density lipoprotein; CVD= cardiovascular disease; BMI= body mass index; DM= diabetes mellitus; FH=familial hypercholesterolemia; ASAT= aspartate aminotransferase; ALAT= alanine aminotransferase; Gamma GT= gamma glutamyl-transferase; LLT= lipid lowering therapy; FH=familial hypercholesterolemia
**1 mmol/l=39 mg/dl † 1mmol/l=89 mg/dl*

Table 2. Effect of PCSK9 inhibitors after 6 weeks follow-up

	Total n=83	HeFH/ Clinical FH n=79	HoFH n=4
PCSK9 inhibitors, n(%)			
Evolocumab	52 (63)	49 (62)	3 (75)
Alirocumab	31 (37)	30 (38)	1 (25)
Lipid values, mean±SD			
• Total cholesterol (mmol/l)*	4.3±2.4	4.1±1.9	7.2±6.5
• LDL cholesterol (mmol/l)*	2.4±2.1	2.3±1.7	5.9±5.5
• HDL cholesterol (mmol/l)*	1.4±0.4	1.4±0.4	1.0±0.3
• Triglyceride (mmol/l)†	1.4±0.9	1.5±0.9	0.9±0.3
• Apo B (g/L)	0.9±0.6	0.8±0.5	1.8±1.8
Glucose (mmol/l)	6.1±2.0	6.2±1.9	5.2±0.3
LDL-C decrease (% mean±SD)	54.9±20.6	55.8±19.8	37.8±31.5
LDL-C ≤1.0 mmol/l*	14 (17)	14 (18)	0
LDL-C by treatment goal, n(%)	48 (58)	47 (60)	1 (25)
• Primary prevention, LDL-C ≤2.5 mmol/l*	18 (55)	18 (23)	0
• Secondary prevention, LDL-C ≤1.8 mmol/l*	30 (60)	29 (37)	1 (25)
Liver tests, mean±SD			
• ASAT (U/L)	27.1±13.4	26.5±12.6	34.3±11.8
• ALAT (U/L)	32.2±29.3	31.0±27.8	30.3±10.6
• Gamma-GT (U/L)	28.5±10.2	29.0±11.4	28.5±12.0
Reactions of PCSK9 inhibitors, n(%)			
Side effects	32 (39)		
Injection site reaction	11 (13)		
Quit PCSK9 inhibitors	7 (8)		
• Side effects	5 (6)		
• Non responders	2 (2)		

LDL=low density lipoprotein; HDL= high density lipoprotein; ASAT= aspartate aminotransferase; ALAT= alanine aminotransferase; Gamma GT= gamma glutamyl-transferase
**1 mmol/l=39 mg/dl † 1mmol/l=89 mg/dl.*

No difference between evolocumab and alirocumab in LDL-C reduction was observed. Genetic heFH patients had less LDL-C decrease compared to patients with clinical heFH (53% vs 67%, p<0.001). The four hoFH patients showed

Table 3. Patient reported side effects of PCSK9 inhibitors

	32 patients (39%)
Any	52
Flu like symptoms	12 (14)
Neurological	8 (10)
Abdominal symptoms	6 (7)
Nasopharyngitis	4 (5)
Allergic skin reactions	4 (5)
Myalgia/joint pain	4 (5)
Headache	4 (5)
Fatigue	3 (4)
Eye irritation	3 (4)
Anxiety attacks	1 (1)
Dysarthria	1 (1)
Flushes	1 (1)
Hoarseness	1 (1)
Discontinuation	7 (8)
Injection site reactions, n(%)	**11 patients (13%)**
Any	16
Hematoma's	4 (5)
Redness	2 (2)
Painful injection	6 (7)
Swelling	4 (5)

an LDL-C decrease of 38% (**figure 1**). Three hoFH patients of whom it was known that they carried ≥1 defective LDLR mutation, showed 50% LDL-C reduction but one hoFH patient with a mutation of unknown effect on LDLR activity did not have any LDL-C reduction. Therefore, we concluded that this patient had no or little residual LDLR function and PCSK9 inhibitor therapy was discontinued. Patients with statin-intolerance had less LDL-C decrease compared to patients who used PCSK9 inhibitors in addition to statin therapy (47% vs 58%, p=0.03). No differences were observed in liver tests or glucose before and after addition PCSK9 inhibitors.

The treatment goal for primary prevention of LDL-C ≤2.5 mmol/L (100 mg/dL) was achieved in 55% of patients without CVD, and the secondary prevention target of LDL-C ≤1.8 mmol/L (70 mg/dL) in 60% of the patients who were known

with CVD. In total 58% of the patients were on-target after addition of PCSK9 inhibitor therapy. Fourteen patients (17%) reached LDL-C levels <1.0 mmol/L (39 mg/dL) (table 2). The lowest LDL-C level measured was 0.31 mmol/L (12 mg/dL), this patient with clinical heFH had a LDL-C decrease of 91%.
On the other hand, 11% (n=9) were hypo- or non-responders defined as a LDL-C decrease ≤25%. Eight of the nine hypo-responders were heFH patients with a pathogenic mutation. They were of similar age and sex compared to the normal responders. In two patients no reduction of LDL-C was observed. One heFH patient with a genetic mutation of the LDLR gene did not respond to PCSK9 inhibitor therapy. The other one was the aforementioned hoFH patient.

Figure 1. Waterfall plot of LDL-C decrease of PCSK9 inhibitors in 79 heterozygous FH patients (each bar represent one patient).

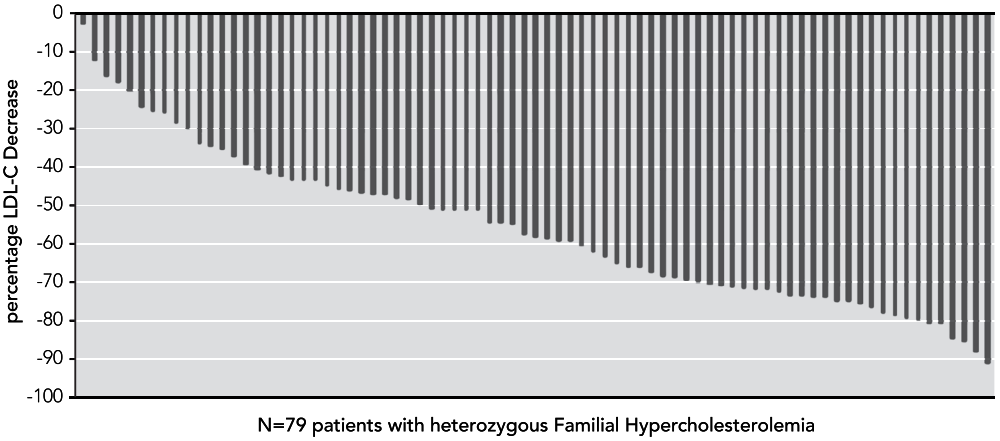
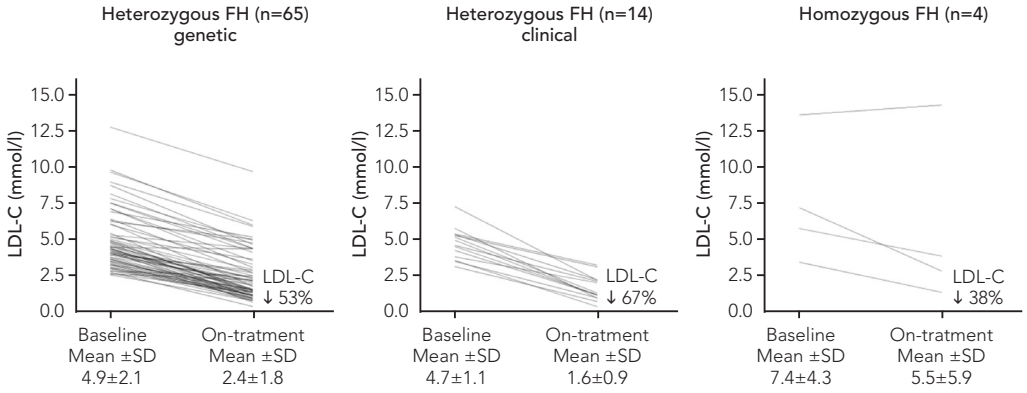


Figure 2. The effect of six weeks treatment with PCSK9 inhibitors according to FH subgroup (HeFH genetic, HeFH clinical and HoFH).



Adherence and side effects

All patients were able to use the auto-injector without any problems. Remembering the unusual interval of administration of the PCSK9 inhibitor every two weeks was mainly implemented through reminders on mobile phone and calendars by patients themselves. All patients confirmed that they were absolute adherent in the use of the PCSK9 inhibitor. Two patients reported technical problems with the injector.

One or more side effects (n=52) of PCSK9 inhibitors were reported by 32 patients (39%) after an average of 6 weeks. Most often flu-like symptoms (14%) in the first days after administrating and abdominal symptoms (7%) were mentioned. Neurological symptoms were reported by 8 (10%) patients, they all reported more than one central or other neurological side effect. Most common were: forgetfulness (n=5), dizziness (n=4), , blurred vision (n=4), confusion (n=2) and depressive mood (n=2). Patients with statin intolerance had significant less side effects (21 % vs 46%, p=0.05) compared to patients who used statins. One or more injection site-reactions were reported by 11 patients (13%), ranging from injection pain (7%) to hematomas (5%) and swellings (5%) on the skin. Seven patients (8%) discontinued treatment; five because of side effects, two patients because of non-response (table 3).

Discussion

We demonstrated that in clinical setting, addition of PCSK9 inhibitors to maximum tolerated LLT showed a similar LDL-C reduction as the randomized clinical trials. The treatment goals of LDL-C ≤2.5 mmol/L (100 mg/dL) for primary and LDL-C ≤1.8 mmol/L (70 mg/dL) for secondary prevention were achieved by 55% and 60% of the patients respectively. However, side effects, especially flu-like symptoms, and injection site-reactions were reported more often compared to clinical trials.

Despite statin-ezetimibe combination therapy, the majority of FH patients fail to attain LDL-C treatment targets. In the Netherlands LDL-C treatment goals are achieved by only 20% of the FH population [10, 11]. Therefore the introduction of PCSK9 inhibitors with its significant LDL-C lowering potential is an attractive additional treatment option for these patients.

The mean LDL-C decrease in our FH population was comparable with randomized controlled trials which studied efficacy of PCSK9 inhibitors in FH patients [14, 15]. The RUTHERFORD I and II randomized heFH patients on stable statin therapy to evolocumab 140 mg (every two weeks) /420 mg (every four weeks) or evolocumab 350 mg (every two weeks) /420 mg (every four weeks) versus

placebo and demonstrated a 43%-55% and 60%-66% reduction LDL-C levels respectively 26, 27. The ODYSSEY FH1 and FH2 trials compared alirocumab 150 mg subcutaneously every two weeks to placebo in heFH patients in addition to high-intensity statin therapy with or without ezetimibe. After 24 weeks a LDL-C reduction of 58% and 51% was observed in the two trials respectively 28. Among heFH patients with LDL-C levels >5.2 mmol/L (201 mg/dL) despite maximum tolerated LLT, the ODYSSEY HIGH FH study showed an LDL-C reduction of 46% after 12 weeks alirocumab 150 mg subcutaneously every two weeks versus placebo [14]. The LDL-C baseline levels of the ODYSSEY HIGH FH study are comparable to the baseline levels of our FH patients, who showed a slightly higher decrease in LDL-C.

None of the clinical trials have so far compared the efficacy of treatment among FH patients with and without genetic mutation. In our study, patients with heFH with pathogenic mutations in LDLR or APOB gene had less LDL-C reduction compared to patients with clinical heFH. While we cannot fully explain this finding, one might speculate that patients with genetic heFH might have a lower expression of LDLR compared to patients with clinical heFH.

Evolocumab is the only PCSK9 inhibitor registered for hoFH patients. The TESLA-B showed that the efficacy of evolocumab 420 mg was dependent on LDLR residual function. While patients with two defective alleles had a 32% LDL-C reduction, in patients with one defective and one null LDLR allele only 21% reduction was observed and patients without LDLR residual function showed no LDL-C reduction. This study therefore provided the evidence that the presence of a functional LDLR is essential for the mechanism of action of PCSK9 inhibitors. The 3 hoFH patients of our cohort with at least one defective LDLR mutation had a 50% LDL-Creduction which is a larger decrease than observed in the TESLA-B study.

Twenty-four percent of our patients used ezetimibe monotherapy because of documented statin intolerance. Three trials have studied the effect of PCSK9 inhibitors vs ezetimibe in patients with statin intolerance. The ODDESSEY ALTERNATIVE compared alirocumab versus ezetimibe. In this study, patients started with 75 mg and if LDL-C target was not achieved after 8 weeks, the dose was increased to 150 mg. The GAUSS-2 and GAUSS-3 studies compared evolocumab 140 mg (every two weeks) and 420 mg (every four weeks) versus ezetimibe. These trials demonstrated an LDL-C reduction of 45%-56% in patients treated with PCSK9 inhibitors and of 17% in patients treated with ezetimibe 29-31. Unlike these trials, our patients with statin-intolerance all used ezetimibe mono-therapy according to the Dutch reimbursement criteria. We

observed a 47% reduction LDL-C in our patients which seems comparable to the trials in patients with statin-intolerance but is lower than patients who concomitantly used statins. This underscores the importance of adherence to statin therapy during PCSK9 inhibitor treatment.
Fourteen patients (17%) reached LDL-C values <1.0 mmol/L (39 mg/dL). These very low LDL-C levels are new to most clinicians and have not been encountered before the use of PCSK9 inhibitor therapy. Recently it was shown that extremely low levels of LDL-C of <0.4 mmol/L (16 mg/dL) do not affect vitamin E and steroid hormone metabolism [32].
On the other hand 42% of the patients did not reach target levels despite PCSK9 inhibitors. This group was predominantly composed of hypo-responders and patients with statin-intolerance who had inadequate LDL-C decrease. This underscores that despite their high efficacy, PCSK9 inhibitors are not the solution for all FH patients.

In the randomized trials, injection-site reactions were reported on average in 6% (range 0-12%),were similar in patients who used a PCSK9 inhibitor and those on placebo, and did not result in discontinuation of the drug. In our study, injection-site reactions were observed more often (13%) than the percentage reported in the trials. However, none of the patients stopped the medication because of injection site reactions.
The randomized controlled trials studying PCSK9 inhibitors showed a very favourable safety profile [33]. In the meta-analysis of 17 trials studying PCSK9 inhibitor therapy the only side effects reported more frequently in patients randomized to PCSK9 inhibitors vs placebo were neurocognitive adverse events (OR 2.34; 95% CI 1.11-4.93). In the five PCSK9 randomized controlled trials in FH patients, side effects were comparable to controls, with most common reported side effects being nasopharyngitis (11%) and influenza (8%) 14, 26-28. In the RUTHERFORD I study, neurological disorders were reported by 5% patients versus 11% controls 26. A recent press release announced that the EBBINGHAUS trial showed no effect on cognitive function in patients randomized to evolocumab compared to placebo [34]. In our study PCSK9 inhibitors were in general well tolerated. However, side effects of flu-like symptoms, neurological symptoms and abdominal symptoms were reported more frequently compared to the heFH trials. For clinicians prescribing PCSK9 inhibitors, it is important to recognize that patients report side effects more often compared to the clinical trials. However only a minority of the patients experiencing side effects discontinued the drug. It should be noted, however, that our patients used PCSK9 inhibitors for a short period. While in long term some side effects could subside,

it is also possible that eventually more side effects will be reported. Therefore, it is important to continue close monitoring of side effects and enquire explicitly for any possible medication-related adverse effects.

The GLAGOV study showed a decrease in Percent Atheroma Volume (PAV) measured by Intravascular Ultrasonography (IVUS) in patients with atherosclerosis treated with PCSK9 inhibitors and statins [35]. Amgen has announced that the FOURIER trial shows a reduction in CVD outcomes in patients randomized to evolocumab compared to placebo. However, details are currently not available [34].

Our study has several strengths and limitations. We have developed a comprehensive database to describe the largest cohort of FH patients treated with PCSK9 inhibitors outside clinical trials to date. Although our patients are treated in a tertiary university hospital, we do consider our results representative of the total FH population who will be candidates for PCSK9 inhibitors. However, we report short-term results in our study. To evaluate side effects, in particular, a larger number of patients during a prolonged treatment period is required.

Conclusions and recommendations

We described our first clinical experience of PCSK9 inhibition in FH patients and showed similar LDL-C reduction but more side effects compared to clinical trials. These findings emphasize the need to establish clinical registries to monitor the long-term efficacy and side effects of PCSK9 inhibitors prescribed outside randomized clinical trials.

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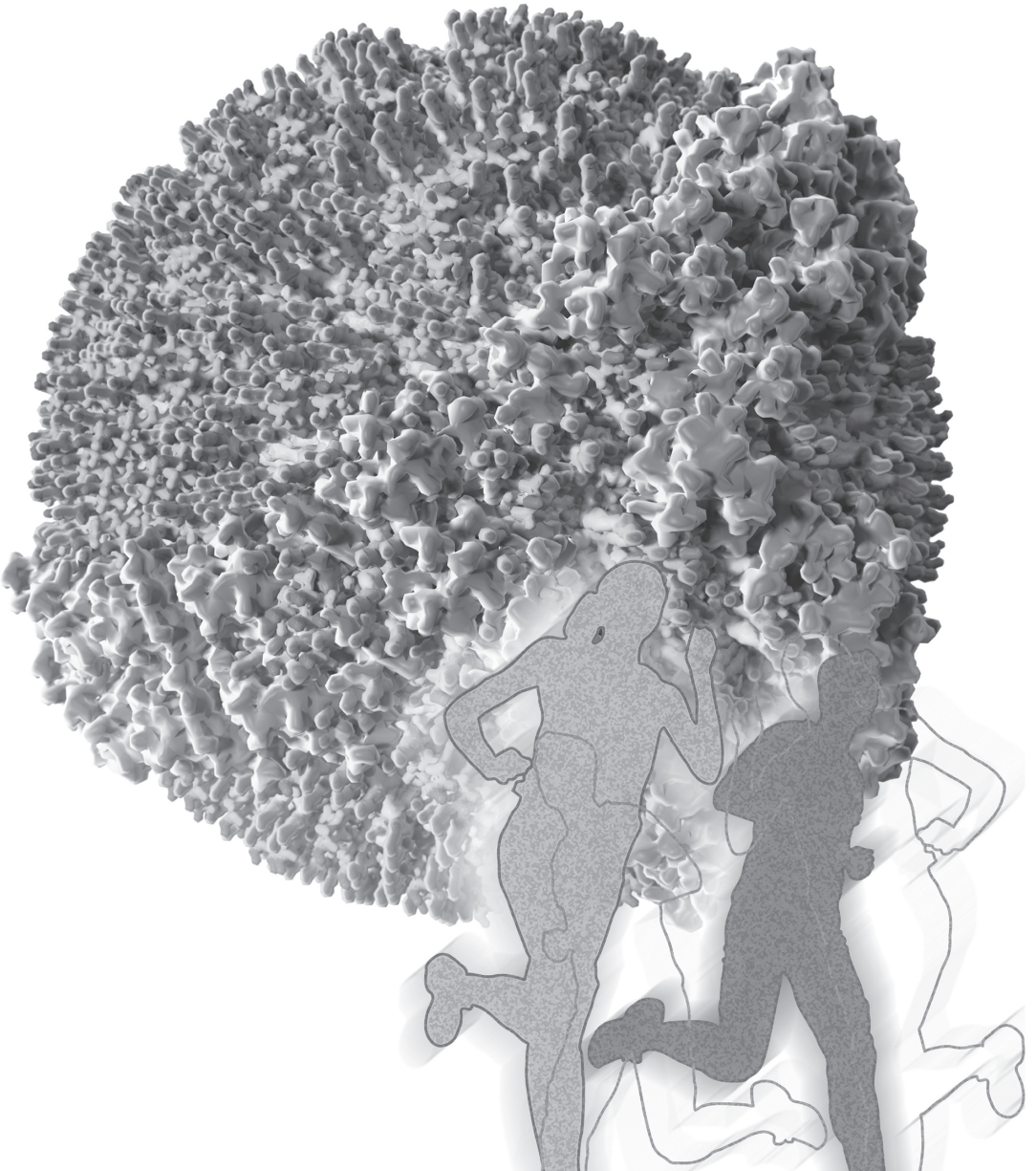
Part 3

General discussion and conclusion



Chapter 8

Conclusions, general discussion and future perspective

General discussion

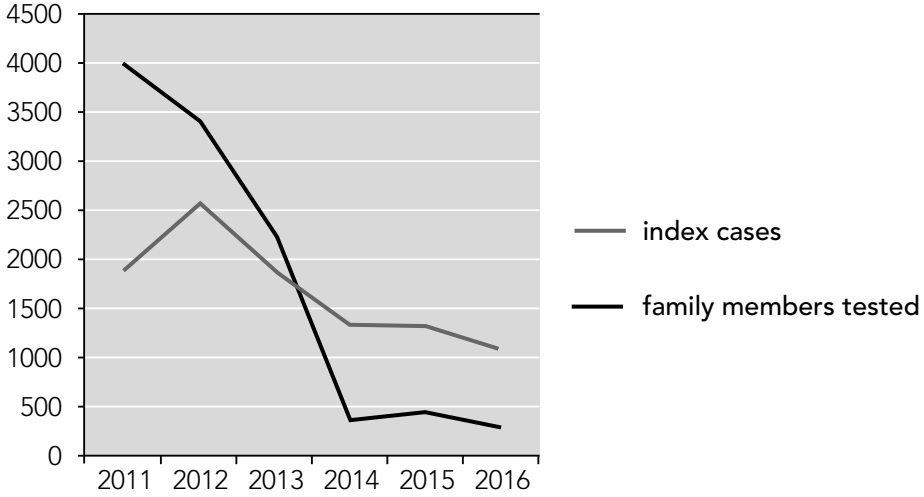
The patients we studied in chapter 3,4,5,6 and 7 were all treated at the cardiovascular genetics (CVG) outpatient clinic in the Erasmus MC. This outpatient clinic is specialized in the diagnosis and treatment of inherited cardiovascular disease (CVD) with a special focus on hereditary dyslipidemia. Patients are referred to the outpatient clinic because they, or first- or second degree relatives, developed premature CVD and/or have dyslipidemia. The clinic is recognized as center of expertise of vascular genetics by the Dutch Federation of University Medical Centers (NFU) and is part of the European Network of Rare Metabolic diseases [1, 2]. In addition, the CVG lipid clinic is official recognized expert centre by Landelijk Expertisecentrum Erfelijkheidsonderzoek Familiaire Hart-en vaatziekten (LEEFH) the national expertise centre for hereditary research of familial cardiovascular disease.

Cascade screening in the Netherlands

Between 2001 and 2014 the national Dutch cascade screening program to diagnose patients with familial hypercholesterolemia (FH) was executed by the Stichting Opsporing Erfelijke Hypercholesterolemie (StOEH). This program was financially supported by the Dutch Ministry of Public Health, Welfare and Sport. Genetic fieldworkers approached family members of the index patient at home, and collected clinical information and DNA blood samples. All data collected during the course of the program, was registered in a central database. Due to end of funding, this national cascade screening program has terminated 1-1-2014. At that moment a total of 28.200 people with FH was identified, 42% of the expected number of FH patients in The Netherlands [3].

Since then LEEFH is responsible for the national coordination for identifying FH families and owner of the national FH database including information of the pedigrees. The most important change since the termination of the national population screening of FH, is that screening and counselling is part of regular insured healthcare. The consequence is that the structure of screening changed from an active to a passive form. Previously, the StOEH actively approached people with FH to test their DNA, nowadays FH patients have to inform their relatives to contact a healthcare provider for DNA testing. This has led to a sharp decrease in the number of detected FH patients (**figure 1**). In **chapter 3** we described that even in the setting of active cascade screening, 20% children with FH are identified because their parent experienced premature CVD. This number is likely to increase if the current trend continues, indicating that active cascade screening must go on.

Figure 1. The number of detected FH patients in the Netherlands



From Louter et al., Atherosclerosis supplements 2017 [4].

Recently a collaboration between organizations of general practitioners (GPs), vascular internists, cardiologists and the Dutch Heart Foundation, is advocating to renew active screening in FH patients [5]. GPs are more and more becoming aware that it is also their responsibility to identify FH in families with high cholesterol (with and without CVD) especially as in clinical practice lipid levels are often initially measured by the GP. But also dermatologists who see patients with xanthomas or ophthalmologist who diagnose an lipoid arcus should be aware to refer these patients to a lipid clinic. Moreover, cardiologists, neurologists and vascular surgeons must be alert of FH, especially in patients with premature CVD. In the end, screening and identification is a joint responsibility of all health care professionals who can encounter FH patients.

The Cardio Vascular Genetic team

The CVG team of the Erasmus MC consists of a lipidologist (internist vascular medicine), a nurse practitioner (NP), fellows vascular medicine, a dietician and two nurses specialized in family counselling. The team collaborates closely with the metabolic paediatrician and cardiologists. Patients are treated by the internist vascular medicine, NP, or one of the fellows vascular medicine. Currently the team has 5 outpatient clinics per week.

Family based approach

The aim of this lipid clinic is to detect and treat people with CVD or inherited lipid disorders at a young age, therefore we advocate a family based approach. When an inherited cause of cardiovascular disease or dyslipidemia is suspected, family counselling is offered by specialized nurses. Treatment is not limited to the patient, but extends to the whole family. Based on this information, pedigrees are made, DNA analyses are performed and results are discussed in the team. Once per week, the whole team has a simultaneous outpatient clinic. Patients can visit multiple members of the team and referral between the team members takes place regularly. Primarily the paediatrician metabolic diseases of the Sophia Children's Hospital treats the children with inherited dyslipidaemias. However, the treating internist also treats children with FH who do not have any comorbidities. Therefore, parents and their children can choose to visit the children's hospital or can combine their appointment at the Erasmus MC outpatient CVG clinic. Our nurses who are specialized in family counselling work both at the outpatient clinics as at the Sophia and Erasmus MC.

Value based health care

In 2015, the CVG team started a project to define value-based care for FH patients. The aim was to organize a care system adding as much value as possible to the treatment of FH patients. In collaboration with FH patients and the Harten Vaatgroep, relevant measurement outcomes have been determined to monitor evidence-based treatment and counselling of patients (personalized healthcare). Using these outcomes, it will be possible to measure and if necessary, improve results of cure and care. Outcome measurements are based on international guidelines and the long term goal is to compare the results of treatment with other centres, but also with other countries in the future. This will enable healthcare professionals to learn from each other and to improve the quality of healthcare.

Prior to the visit of the out-patient clinic, patients are send digital validated questionnaires; a quality of life questionnaire, (EQ-5D-5L, Dutch version), a medication adherence questionnaire (MARS5), a FH knowledge questionnaire and a self-efficacy and motivation questionnaire. The treating physician and NP prepare and interpret the answers of the questionnaires and discuss these with the patients during consultation. All results of the questionnaires are collected in a database.

Management of patients with familial hypercholesterolemia

Patients with FH are treated according to recommendations of the European guideline for the management of dyslipidaemias [6]. Treatment is life-long and consists of two main components: lipid lowering therapy (LLT) and lifestyle modification. Healthcare providers focus on an integrated approach; medical treatment and lifestyle intervention by promoting self-management.

Promoting self-management

LLT is considered the cornerstone of treatment of FH patients. Therefore good adherence is essential (chapter 5). This means using medication according to the prescription. In addition, adults and children with a hereditary dyslipidemia are advised to live healthy, to eat healthy, to exercise sufficiently, to maintain a healthy weight and the most important life style advice: to avoid smoking. This health behaviour can be considered as self-management.

In our team, the NP is specifically trained in supporting self-management in FH patients. It is the most essential part of nursing chronically ill people [7]. Self-management has many descriptions but Barlow, who is considered an expert in the field, explained that there is no golden standard. The definition can be described as the individual ability to deal with symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent to live with a chronic condition [8]. Providing knowledge about the disorder is necessary for adequate self-management, however knowledge alone is not enough. By clarifying behaviour of patients (insight), understanding and awareness can be created. This is the first step of behavioural change for a healthy lifestyle. Self-efficacy and motivation are important factors in this process. A high level of self-efficacy and motivation is supportive in changing behaviour [9].

Knowledge

To promote knowledge, the CVG team organizes educational meetings for patients and their relatives about FH, cardiovascular risk factors, lifestyle modification and new developments in treatment modalities. Patients are invited as expert speakers to share their experiences. Another way of providing knowledge are the posters which our team have developed and are shown in the waiting room of the out-patient clinic, depicting targets for lipid levels, blood pressure, weight, importance of not smoking, eating healthy and doing regular exercise.

Motivation and self-efficacy

The level of motivation and self-efficacy is measured by specific questionnaires. Motivation and self-efficacy can be influenced by interventions of the treating healthcare professionals, for example by creating realistic behavioural goals and complimenting all positive aspects regarding achieved results of lifestyle improvement. But also by supporting patients to learn from each other and to organize social support from relatives [10]. Finally, to promote and influence the level of self-efficacy and motivation, positive feedback is given when lipid levels, blood pressure, weight or medication adherence have improved. Laboratory results as well as blood pressure and BMI are printed, discussed and handed to the patients to take home. It is Important that the patient is in the lead, together with the healthcare provider achievable goals are discussed and agreements for future goals are made. To stimulate patients to improve their lifestyle it is necessary to ensure that follow-up is provided. The treatment is based on the relationship of the healthcare provider with the patient and his/her relatives, with respect for autonomy. In this way, care and cure are integrated from patients' perspective.

Self-management in children with familial hypercholesterolemia

Although there are different points of view about the exact age of starting treatment with lipid lowering medication in children with FH, it is well established that the process of atherosclerosis begins in early childhood [11]. In agreement with the European consensus for management of children with FH, the CVG team of the Erasmus MC prefers to perform genetic testing and if necessary treat children with LLT before the age of 10 years if one of the parents is diagnosed with FH [12]. The background of treating FH children before the age of 10 has two main reasons. First to start stimulating a healthy lifestyle at a young age and second to measure lipid levels to timely start lipid lowering treatment to delay the process of atherosclerosis [13].

Promoting a healthy life style in children

Maintaining a healthy lifestyle is not always easy for young FH patients. They are exposed to all kinds of temptations such as smoking, drinking alcohol, unsafe sex and unhealthy diet. When children smoke between the age of 14 and 20 years, it is very difficult for them to quit this addiction [14]. At this age, smoking behaviour is mostly influenced by peers while the influence of their parents decreases significantly [15]. On the other hand, young children between 8-12 years old, still have a negative attitude towards smoking. They describe smoking as

"dirty" and "unhealthy". This attitude needs to be strengthened by explaining young people why the combination of smoking and FH enhances cardiovascular risk [16]. Healthcare professionals can help children to make a proper risk assessment of behaviour. By giving understandable tailored information about smoking in order to reinforce the natural negative attitude concerning this behaviour. Not only the disadvantages of smoking, but also the advantages of healthy behaviour, such as sports and maintaining a healthy weight and diet, need to be discussed [17]. In addition, before children go to high school, they must be able to resist influences from their environment. Children need to have enough self-confidence (self-efficacy) to say "no" to friends offering cigarettes by developing their own opinion and identity on this topic. A high degree of self-efficacy is necessary to change behaviour, for example the intention to avoid or stop smoking [9]. It is custom in our outpatient clinic to make an agreement not to start smoking between the child and the treating healthcare professional at the end of each appointment. In the end: prevention is always better than cure.

Self-management in adults with familial hypercholesterolemia

Since a few decades, statins are the first choice treatment for patients with FH. LLT by statins is effective in lowering LDL-C levels. CVD risk has decreased substantially since statin treatment became available, but despite maximum treatment for many years, 12% of patients still develop CVD (chapter 4). This is noteworthy because in our clinic 90% of the patient use maximally tolerated lipid lowering therapy: almost two-thirds of the adult FH population (61%) at our outpatient lipid clinic are currently treated optimally with statins, 29% uses maximum tolerated LLT because of side effects. We showed that those patients who still develop CVD, are not patients with as only risk factor LDL-C levels not on target, but especially those patients who have other risk factors such as smoking or hypertension have an increased risk of CVD (chapter 4). The question is if more potent lipid lowering medication, such as Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) inhibitors, will be the solution for abolishing cardiovascular risk.

Investment in lifestyle modification

Patients and healthcare professionals should invest more in lifestyle modification. There is still much to be gained in investing in a healthy lifestyle, such as quit smoking- or even better smoking prevention- than increasing medication. Recently Kehra, et al., showed that a healthy lifestyle in patients with a genetically increased CAD risk was associated with a nearly 50% lower relative risk of

CAD compared to an unfavourable lifestyle [18]. Chow et al., showed in a randomized lifestyle intervention study in CAD patients that adherence to diet, physical activity, and smoking cessation was associated with a decreased risk of cardiovascular events. Those who reported persistent smoking and non-adherence to diet and exercise had a nearly 4-fold increased risk of myocardial infarction/stroke/death compared to never-smokers who modified diet and exercise [19]. However, achieving optimal health behaviour is a challenge for both patients and healthcare professionals. Smoking is a major avoidable risk factor. The most effective treatment to stop smoking is a combination therapy of intensive intervention of pharmacotherapy and behavioural support [20]. However, the most important part consist of motivation to stop smoking. Healthcare providers should investigate more time in this first step of therapy, not only by communicating that patient must stop smoking. Personalized goals to quit smoking need to be investigated and discussed.

The results of the specialized stop smoking outpatient clinic of the Erasmus MC showed comparable outcomes to stop smoking methods used in randomized trials [21]. Although 23% did not resume smoking after one year, the results of smoking cessation in general are not very successful. However, lifestyle modification remains essential to improve patients' cardiovascular outcome. Therefore, treatment of FH patients should not only focus on optimizing LDL-C levels, but also on improving other CVD risk factors **(chapter 4)**.

Medication adherence

FH patients have a chronic condition, they have to live with FH the rest of their life. They don't have any physical symptoms, but need to take preventive medication life-long. Only 19% of our FH patients, achieved their LDL-C treatment goal. We assessed whether non-adherence and factors associated with non-adherence in **chapter 5**. Non-adherence of statins was reported in 11% of the patients. Those patients who were non-adherent, were younger and used statins more recently than those who were adherent. Moreover, they showed higher levels of treated LDL-C-and total cholesterol and had a lower untreated baseline total cholesterol [22]. Especially young people (18-35 years old) found it difficult to use medication daily. They have to do something (daily intake of medication) for their future, while they don't have any symptoms at this moment. In addition, medication adherence is not static but a continuous life-long process [23]. Therefore, during every visit patients should be asked about their medication intake without judgement. We developed a risk score based on age and lipid values which can help to assess the risk of non-adherence **(chapter 5)**. The cause of

non-adherence varies and has to established individually. There is no standard solution for this problem. Individual causes for non-adherence such as the level of health literacy, developing skills to take responsibility or to think abstractly, have to be established and to discussed together with the patient to find a tailored suitable solution [24].

New medication; Proprotein Convertase Subtilisin/Kexin 9 inhibitors

PCSK9 inhibitors are reimbursed in the Netherlands since 2016. Currently two PCSK9 inhibitors are available; evolocumab (140 mg sc once per 2 weeks or 420 mg once per 4 weeks for homozygous FH patients) and alirocumab (75 mg or 150 mg sc once per 2 weeks). PCSK9 inhibitors are associated with impressive LDL-C reductions and a favourable safety profile [25,26]. The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) study showed a mean LDL-C reduction of 59% and a 15% reduction in CVD events in high risk CVD patients using evolocumab 140 mg per 2 weeks or 420 mg per 4 weeks compared to placebo [27].

PCSk9 inhibitors are currently reimbursed for patients at very high risk of CVD who do not reach LDL-C treatment targets despite maximum tolerated LLT. FH patients are considered to belong to this category Homozygous FH patients who carry two LDLR negative mutations are not suited for this therapy as residual LDLR activity is mandatory for its effect. Maximum tolerated LLT also applies for heFH patients with documented statin intolerance defined as statin-associated myalgia for at least three different statins in accordance with the flow chart described by EAS/ESC consensus who use ezetimibe monotherapy [28]. We show that heFH patients who use a PCSK9 inhibitor in combination with statin and ezetimbe show similar decreases in LDL-C compared to clinical trials **(chapter 7)**. At baseline, only 19% of FH patients achieved the LDL-C target (LDL-C ≤2.5 mmol/l for primary prevention or LDL-C ≤1.8 mmol/l for secondary prevention), with the addition of a PCSK9 inhibitor the percentage of patients reaching LDL-C target increased to 58% **(chapter 7)**. FH patients in our cohort showed large variation in LDL-C decrease, ranging from 10% to 90%. An additional analysis between the hypo responders and hyper responders (≤25% - ≥75% decrease) showed that LDL-C decrease was larger in FH patients without known genetic mutations compared to FH patients with a known pathogenic mutations. An explanation for this finding could be the reduced residual function of LDL receptors in FH patients with a genetic mutation. Another possible explanation for this variation could be the PCSK9 level in patients. If patients have higher PCSK9 levels , more PCSK9 can be bound, possibly resulting in a more pronounced

LDL-C decrease. Future studies measuring PCSK9 levels will establish if this hypothesis is true.

Promoting self-management and PCSK9 inhibitors

Initially we had concerns about lifestyle adherence in patients who started with PCSK9 inhibitors. The impressive decrease in LDL-C levels could potentially negatively affect the maintenance of a healthy lifestyle. However patients were re-encouraged to investigate in lifestyle-modification. A few patients quit smoking after 30 years, some performed a higher level of exercise and others focused more on a healthy diet or on medication adherence, demonstrating that motivation of patients to change their behaviour is not a fixed situation. Despite the impressive decrease in LDL-C as a result of PCSK9 inhibitor therapy, not all patients achieved target levels. The mean BMI in our FH population was 27.3±4.0 kg/m^2. Being overweight was not associated with not achieving treatment goals. However lifestyle modification should persistently be integrated in the treatment of FH patients (chapter 7).

All patients who start with a PCSK9 inhibitor are invited for a group consultation led by the NP. Prior to the first subcutaneous injection of the PCSK9 inhibitor, patients and their relatives receive information how this new drug works and get instructions how to administer this auto-injector. In addition patients are educated to continue all current medication and to maintain a healthy lifestyle, practical issues such as vacations and adherence to this unusual administration schedule are addressed.

A new experience; how low can you go?

PCSK9 inhibitor regiment pose healthcare professionals and patients for new challenges: namely the very low LDL-C levels which can be achieved. Seventeen percent of the patients who started with a PCSK9 inhibitor reached LDL-C levels of <1.0 mmol/l) (chapter 7). Currently it is not known whether a threshold exist below which further LDL-C reduction is not beneficial anymore or can even be harmful. Therefore, in some patients with LDL-C levels <0.6 mmol/l the decision was made to reduce the dose or increase the interval of the PCSK9 inhibitor. Blom et al., showed that in patients using evolocumab vitamin e and steroid levels are not reduced even in patients who reach LDL-C levels <0.4 mmol/L. As in the near future many patients who use PCSK9 inhibitors will encounter very low LDL-C levels, close monitoring for instance via a registry will be important to assess long term effects [29].

Adverse drug reactions of lipid lowering therapy

In our experience we found slightly more side effects attributed to PCSK9 inhibitors in clinical practice compared to clinical trials (chapter 7). There were no differences in side effects between men and women. In particular, neurological side effects were a reason for stopping PCSK9 inhibitors. Initially a minimal but significant increase in neurocognitive side effects was reported in a meta-analysis of all PCSK9 inhibitor trials [30]. However, the EBBINGHAUS study (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) showed that there was no association between the cognitive function of patients with a cardiovascular event and the use of a PCSK9 inhibitor [31]. Our patients also experienced more symptoms of flu-like symptoms and abdominal complaints. A reason for this overrepresentation of side effects could be the fact that all patients were informed about side effects of this medication prior to the first administration [32]. At present, patients use internet and search for information more often. It should be noted that all complaints have been reported by the patients themselves and in some patients it was uncertain if the reported side effects were associated with the PCSK9 inhibitors. In collaboration with the Landelijke registratie evaluatie bijwerkingen (Lareb), the Dutch Pharmacovigilance and knowledge centre for adverse drug reactions, we will continue to monitor possible adverse drug reactions carefully.

We did find gender differences in side effects of statin therapy (chapter 6). While there was no gender difference in the overall percentage of patients who reported any side effect, women were more likely to report having experienced three or more side effects. Also a larger proportion of them reported severe impact of statin therapy on their quality of life. However, women received less often maximum statin therapy compared to men (chapter 6). Because side effects might influence adherence to treatment, it is important to address this issue regularly as health care provider.

Future perspective

New guideline for patients with FH

Currently a guideline committee has developed a new national multidisciplinary guideline on dyslipidemia with a focus on FH, which describes how to detect and treat those people and their first and second degree relatives. Often the general cardiovascular risk Management (CVRM) guideline is incorrectly utilized in these patients, resulting in insufficient or no treatment at all of FH patients. This general guideline for cardiovascular disease prevention is not applicable to patients with hereditary dyslipidemia because the absolute risk is higher than

the population risk chart (SCORE) used in the guideline [33]. Collectively, cardiologists, the paediatricians, the internists and GPs are involved in the detection and treatment of people with FH. The ultimate aim is to maintain the quality and efficacy of FH care in The Netherlands and the expectation is that the new guideline will be able to help to achieve this goal.

Medication adherence in children

Children up to 18 years have not been examined in our study assessing adherence to lipid lowering medication **(chapter 5)**. Children who have other chronic disorders, such as asthma or diabetes mellitus type 2, show a high percentage of non-adherence. The percentage of medication adherence in chronically ill children with the above mentioned disease varies, but the adherence is predominantly low. Adherence of medication decreases as the age increases [34, 35]. Adolescence is a strong predictor of non-adherence. Many factors are associated with non-adherence in children [24]. Importantly, there is a clear relationship between non-adherence and poor outcome of disorders described in literature [36]. Successful interventions to improve medication adherence in children are not available [37]. In case of unconsciously forgotten medication, sending text messages seems to be effective. But when medication is not used consciously, this intervention will not work. Therefore, improving medication adherence and discovering factors associated with non-adherence in children remains an important topic for the optimal treatment of children [38].

Collaboration with other partners

In the near future, the cardiovascular center will be established in the Erasmus MC in collaboration with the department of cardiology, internal medicine, thorax surgery and vascular surgery. One of the focuses will be an integrated approach focused on secondary prevention coordinated by nurses. These CVD prevention programs, in particular in up-titration of medication, have proven to be successful [39]. Lipid levels and blood pressure were more often on target in CVD patients after intervention of a nurse, although the impact on lifestyle risk factors remained limited. Collaboration with other partners in coaching of weight control by Weight Watchers, stop smoking by trained professionals and developing instruments for a more physical active lifestyle by Philips DirectLife seems to be effective [40]. To improve cardiovascular risk management according to guidelines, healthcare professionals and patients are advised to cooperate with these new partners in healthcare.

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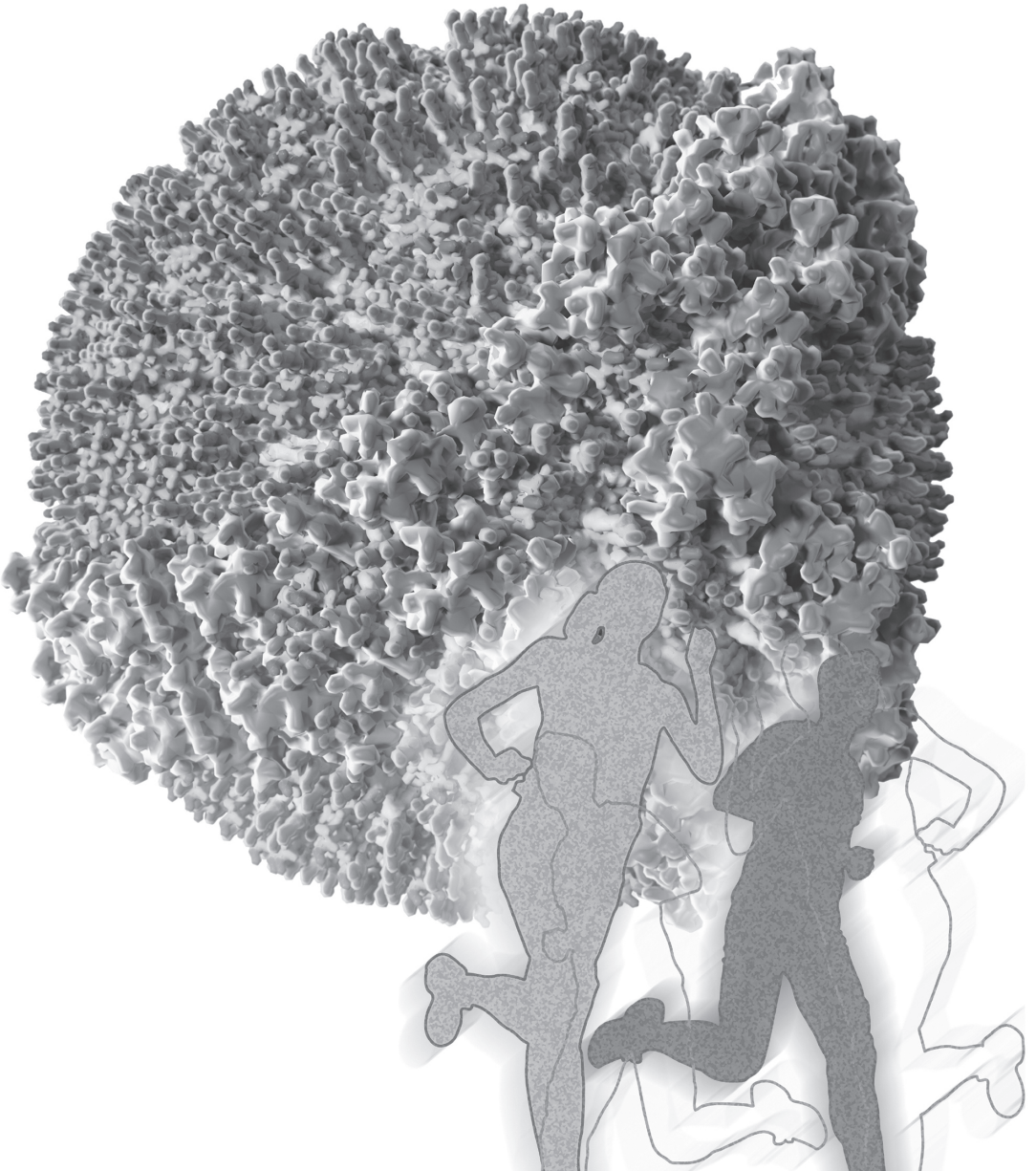


Chapter 9
Summary/Samenvatting

Familial hypercholesterolemia (FH), is an autosomal dominant disorder of the lipid metabolism with a prevalence of 1:244 in The Netherlands. FH is caused by pathogenic mutations in the low-density lipoprotein receptor (LDLR), Apolipoprotein B (APOB) or PCSK9 gene and characterized by high levels of LDL-Cholesterol (LDL-C) leading to high/severe risk of cardiovascular disease (CVD) at premature age. Prevention of CVD consist of the combination of lipid-lowering therapy and lifestyle modification.
In this thesis, we studied several parts of the management of patients with FH. In the first part of this thesis we studied the diagnosis and risk prediction of patients with FH.

Chapter 2 describes the usefulness and necessity of lipid testing. Why should we test lipids, who should we test according the guidelines and when should we test lipids. Important to every clinician should be the question: What do the results mean to my patient? A systematic risk stratification to identify those at the highest risk is required. European, British and American guidelines are all based on a risk calculator but differ in their recommendations concerning lipid testing. What they have in common is that they advocate an integrated approach with the engagement of the patient as a partner in cardiovascular disease (CVD) prevention. Nonetheless, despite all guidelines, in the end decisions concerning lipid testing are about communication with the patient involving individual circumstances including why, who and when.

Chapter 3 describes the setting of cascade screening of patients with FH in The Netherlands and specially the screening of children with FH. The national cascade screening programme has terminated at the end of 2013. This study reports that 1:5 children with FH are identified because their parent experienced CVD, mostly at a premature age. The fact that CVD is still a presenting event of FH in especially fathers, shows that nationwide screening might have been terminated too early. To prevent CVD, the next generation should be in clinical attention to start statin treatment and a healthy lifestyle in time.

Chapter 4 describes that despite effective treatment with optimal lipid lowering treatment (LLT) patients with FH still develop CVD. We showed that 12% of patients still develop CVD and identified individuals at high risk in a cohort of 821 heterozygous adult FH patients using long time LLT. We demonstrated that the residual risk of cardiovascular events consist of 16 events per 1000 statin-treated person years. Almost one third of those patients with a cardiovascular event,

developed a subsequent event, underlining the need for CVD prevention in this population. In addition to lipid parameters, classical risk factors, especially smoking and hypertension, contributed to the developing of cardiovascular events during LLT. Therefore, treatment of FH patients should not only focus upon optimizing LDL-C levels, but also on improving other CVD risk factors.

In the second part of this thesis, the management of patients with FH is described.

Chapter 5 describes the development of a prediction model to identify non-adherent FH patients. The results of this study demonstrate that statins reduced the untreated total cholesterol level by 46% in our heterozygous FH study population. In only 19% of patients the treatment goal was achieved. We assessed whether these results were influenced by the factor of non-adherence. Non-adherence of statins was reported in 11% of the patients. They were younger and shorter on statin prescription. They showed higher treated LDL- and total cholesterol levels and had a lower untreated baseline cholesterol. Based on these independent variables, a non-adherence risk score calculator was developed to assess and improve adherence in clinical practice during patient consultation.

Chapter 6 reported gender differences in lipid profile, lipid lowering therapy, statin adverse effects, and factors associated with treatment effectiveness in a well-defined cohort of patients with FH. This study highlights the lower likelihood for women to receive high-intensity therapy despite their poorer baseline lipid profile and emphasizes the negative impact of statin side effects on achieving the desirable clinical outcomes among women.

Chapter 7 described the first clinical experience of a recently new class of lipid-lowering therapy; Proprotein Convertase Subtilisin / Kexin 9 (PCSK9) inhibitors in FH patients. Outside clinical trials the efficacy and side effects of PCSK9 inhibitors is evaluated and showed similar LDL-C reduction but more side effects and injection site reactions compared to clinical trials in FH patients.

Familiaire hypercholesterolemie (erfelijk verhoogd cholesterol, FH), is een autosomaal dominante afwijking van het lipidenmetabolisme en komt bij 1:244 mensen in Nederland voor. FH wordt veroorzaakt door pathogene mutaties in de low-density lipoprotein (LDL) cholesterol receptor, Apolipoprotein B (APOB) of het Proprotein convertase subtilisin/kexin 9 (PCSK9) gen. Deze aandoening wordt gekenmerkt door hoge LDL-Cholesterol waarden vanaf de geboorte en leidt onbehandeld tot een hoog risico van hart-en vaatziekten op jonge leeftijd. Preventie van hart-en vaatziekten bij deze mensen bestaat uit een combinatie van lipidenverlagende medicatie en leefstijlaanpassingen.
In deze thesis, zijn verschillende onderdelen van management van zowel de medische behandeling als de verpleegkundige zorg van FH patiënten bestudeerd. In het eerste onderdeel werd het stellen van de diagnose FH en het voorspellen van risico's bij FH patiënten bestudeerd.

Hoofdstuk 2 beschrijft het nut en de noodzaak van het testen van een lipidenprofiel. Waarom zouden we lipiden moeten testen, wie zouden volgens de richtlijnen hun lipiden moeten laten testen en wanneer zou iemand zijn lipidenwaarden moeten laten testen. De belangrijke vraag voor elke behandelaar moet steeds zijn; wat leveren de resultaten op voor mijn patiënt? Een systematische risico-stratificatie is vereist om juist degenen met het hoogste risico te kunnen identificeren. Europese, Britse en Amerikaanse richtlijnen zijn allemaal gebaseerd op een risicoberekening, maar verschillen in hun aanbevelingen voor het testen van lipiden. Wat zij gemeen hebben, is dat zij een geïntegreerde aanpak bepleiten waarbij de betrokkenheid van de patiënt als partner in preventie van hart- en vaatziekten voorop staat. Toch, ondanks alle richtlijnen, beslissingen met betrekking tot het testen van lipiden worden genomen op basis van communicatie met de patiënt gebaseerd op individuele omstandigheden, waaronder waarom, wie en wanneer.

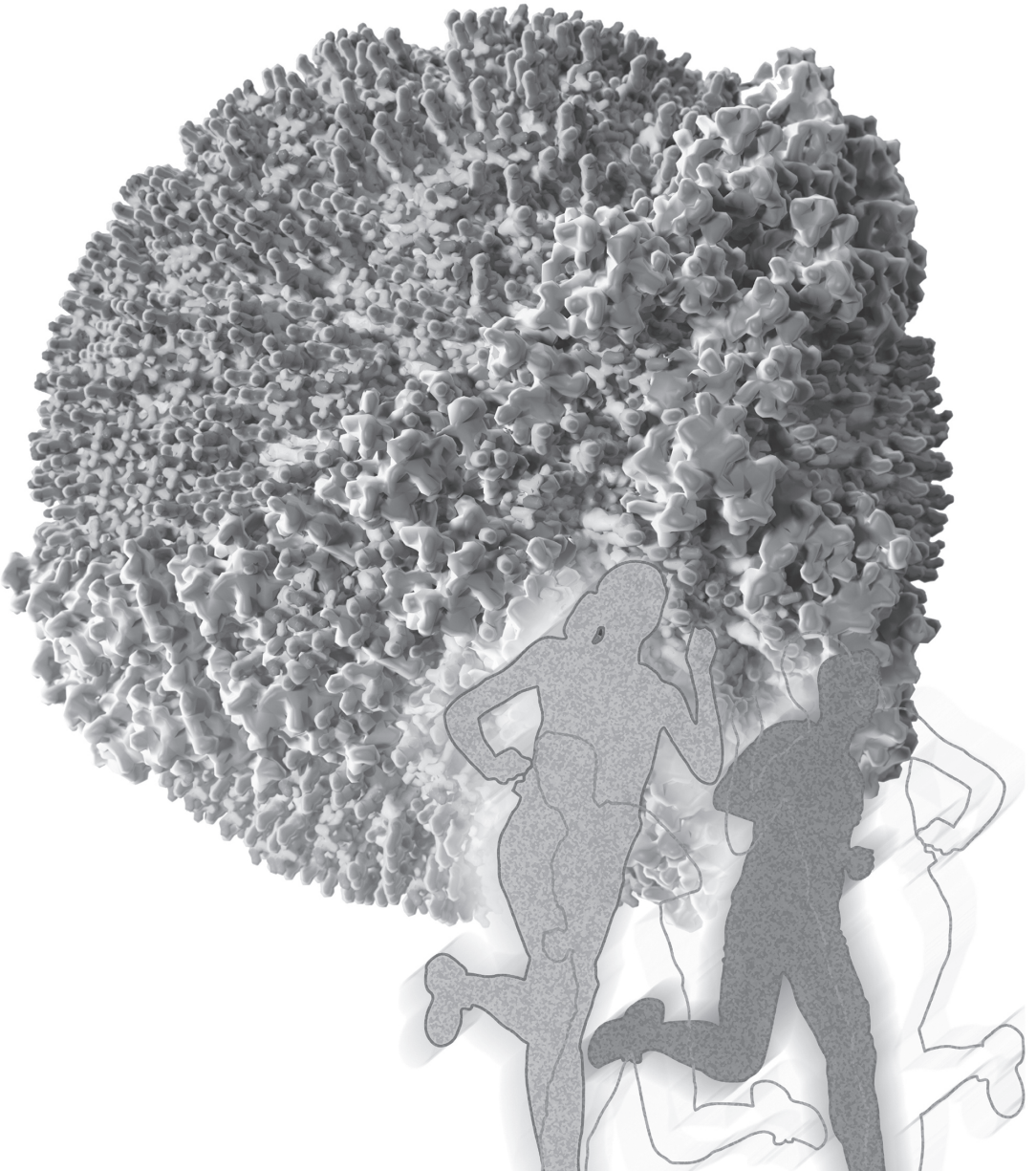
Hoofdstuk 3 beschrijft de achtergrond van de cascade-screening van patiënten met FH in Nederland en speciaal de screening van kinderen met FH. Het nationale cascade screening programma is eind 2013 afgesloten. Deze studie vermeldt dat 1:5 kinderen met FH wordt geïdentificeerd omdat hun ouders hart-en vaatziekten hebben doorgemaakt, meestal op premature leeftijd. Het feit dat hart-en vaatziekten zich nog steeds voordoet in vooral vaders met FH, veronderstelt dat het landelijke screeningsprogramma mogelijk te vroeg is beëindigd. Om hart-en vaatziekten te voorkomen, dient de volgende generatie op tijd in beeld te worden gebracht om de behandeling met statines en een gezonde leefstijl tijdig te kunnen starten.

Hoofdstuk 4 beschrijft de uitkomsten van een effectieve behandeling voor lange tijd met stabiele lipidenverlagende medicatie bij patiënten met FH. In een cohort van 821 heterozygote volwassen FH patiënten is onderzocht hoeveel patiënten hart-en vaatziekten ontwikkelen, daarnaast is gekeken welke risicofactoren daarop van invloed zijn. We hebben aangetoond dat het resterende risico op het verkrijgen van cardiovasculaire gebeurtenissen 12% is (16 events per 1000 statine behandelde persoons jaren). Bijna een derde van deze patiënten met een cardiovasculair event ontwikkelde een tweede event, daarmee werd de noodzaak van hart-en vaatziekten preventie in deze populatie nog meer onderbouwd. Naast lipidenparameters, dragen klassieke risicofactoren als roken en hypertensie, bij aan de ontwikkeling van hart-en vaatziekten tijdens lipidenverlagende therapie. Daarom dient de behandeling van FH-patiënten zich niet alleen te richten op het optimaliseren van het LDL-Cholesterol, maar ook op het verbeteren van overige risicofactoren van hart-en vaatziekten.
In het tweede deel van dit proefschrift wordt het management van patiënten met FH beschreven.

Hoofdstuk 5 beschrijft de ontwikkeling van een voorspellingsmodel om niet-therapietrouwe FH patiënten te identificeren. De resultaten van deze studie laten zien dat statines het onbehandelde totale cholesterol met 46% verlaagd in deze heterozygote FH studie populatie. Bij slechts 19% van de patiënten werd het behandeldoel LDL-C ≤2.5 mmol/l bereikt. We hebben onderzocht of het niet trouw innemen van de medicatie van invloed was op het bereiken van deze streefwaarde. Therapie-ontrouw van statines werd gerapporteerd in 11% van de patiënten. Ze waren jonger en gebruikten korter een statine. Zij toonden hogere behandelde LDL-en totaal cholesterolwaarden en hadden een lager onbehandeld baseline cholesterol. Op basis van deze onafhankelijke variabelen is een risicoscore calculator voor therapie-ontrouw ontwikkeld om in de klinische praktijk therapie-ontrouw beter te kunnen beoordelen en daar waar mogelijk te verbeteren.

Hoofdstuk 6 rapporteert in een goed gedefinieerd cohort van patiënten met FH verschillen tussen mannen vrouwen in het lipidenprofiel, de lipidenverlagende therapie, bijwerkingen van statines en factoren geassocieerd met de effectiviteit van de behandeling. Deze studie toont aan dat vrouwen minder vaak hoge doseringen statinetherapie krijgen voorgeschreven ondanks hun hogere onbehandelde lipidenwaarden in vergelijking tot mannen. Tevens wordt de negatieve impact van bijwerkingen van statines op het bereiken van het gewenste klinische resultaat onder vrouwen benadrukt.

Hoofdstuk 7 beschrijft de eerste klinische ervaring van een nieuwe klasse lipiden verlagende therapie; Proprotein Convertase Subtilisin / Kexin 9 (PCSK9) remmers bij FH patiënten. Buiten klinische studies is de werkzaamheid en de bijwerkingen van PCSK9-remmers geëvalueerd. Deze FH patiënten lieten een vergelijkbare LDL-C reductie zien maar vertoonden meer bijwerkingen en injectie reacties vergeleken met de klinische studies.



Chapter 10

PhD portfolio
About the author
Dankwoord
List of peer reviewed publications

Name:	Annette Galema-Boers
Erasmus MC Department:	Internal Medicine
Research School:	COEUR
PhD period:	2014-2018
Promotor	Prof. dr. J.L.C.M. van Saase
Supervisors:	dr. J.E. Roeters van Lennep, dr. M.J. Lenzen

1. PhD training

	Year	Hrs/ECTS
Research skills		
Methodology of research and preparation of grant applications.	2009	1
Course critical reading of articles.	2011	1
Statistics and Survival Analysis for MD.	2010	1
Basic Introduction Course SPSS.	2010	1
GCP registration (BROK) course.	2015	1
		Total 5
International Presentations		
Spring Meeting, ESC; An example of a nurse led lipid clinic, Sweden.	2008	1
Cardiovascular Nursing in the Netherlands, Athene.	2008	1
Annual congress ESC; Predicting adherence of FH patients, Paris.	2011	1
Patients with FH in the Netherlands, Houston.	2013	1
Euro Heart Care; Cascade screening must go on, Dubrovnik.	2014	1
Euro Prevent; Residual cardiovascular risk in FH patients, Malaga.	2017	0.5
Euro Prevent; PCSK/9 inhibition in patients with FH, Malaga.	2017	0.5
Euro Heart Care; Residual cardiovascular risk in FH patients, Sweden.	2017	0.5
Euro Heart Care; PCSK/9 inhibition in patients with FH, Sweden.	2017	0.5
Wetenschapsdagen; Residual cardiovascular risk in FH patients, Belgie	2017	
		Total 7
National Presentations		
Annual congress V&VN VS; Workshop about cholesterol.	2015	1
Annual congress V&VN VS; Residual cardiovascular risk.	2016	1
CarVasZ; Cascade screening must go on.	2015	1
Nationale lipidendag PCSK9 remming: De eerste Nederlandse ervaringen.	2016	0.5
CarVasZ; Residual cardiovascular risk in FH patients.	2016	1
GP's; Residual cardiovascular risk in FH patients and PCSK/9 inhibitors.	2017	1
CarVasZ; Instrueren van patiënten met PCSK/9 inhibitor	2017	0.5
CarVasZ; Cholesterol verlaging wat hebben we tot nu bereikt	2017	0.5
Erasmus MC; Nieuwe cholesterol verlagende middelen	2017	0.5
		Total 14
Seminars and workshops		
Spring Meeting ESC, Brussel.	2011	1
Annual congress ESC, Amsterdam.	2013	1
Annual congress ESC, Barcelona.	2014	1
Annual congress V&VN VS.	2014	0.6
Annual congress V&VN VS.	2015	0.6
Annual congress V&VN VS.	2016	0.6
Harvard University Lipid management, Boston.	2016	0.9
Coeur course Cardiovascular imaging and diagnostics.	2017	0.5
		Total 6.2

2. Teaching activities	Year	Hrs/ECTS
University of applied sciences Rotterdam		
Promoting self-management	2014-2015	1
Teaching patients how to use PCSK9 inhibition	2015-2017	0.5
Lecturing		
Lectures at meetings for FH patients and caregivers	2009-2015	1
Supervision		
Nurse teacher of MANP student	2014	0.5
Other		**Total 3**
President of the Dutch National Society of Cardiovascular Nursing (NVHVV).	2005-2008	3
Board member of the Dutch National Society of Cardiovascular Nursing.	2008-2011	2
Board member The National Society committee of the Council Cardiovascular Nurses and Allied Professions (CCNAP) of the ESC.	2007-2009	1
Board member of the Accreditation Committee NVHVV.	2010-2015	2
President of the expert group of Nurse Practitioners NVHVV.	2013-2016	1
President of nurse practitioners and physician assistants section of the Erasmus MC.	2015-present	1
Professional membership		**Total 10**
Dutch National Society of Cardiovascular Nursing (NVHVV).		
Dutch Society of Nurse specialists (V&VN-VS).		
The Union (NU'91).		
Council of Cardiovascular Nurses and Allied Professions (CCNAP) of European Society of Cardiology (ESC).		

About the author

Annette Galema-Boers was born in Zoeterwoude on February 7th, 1964. After graduating high school (HAVO) in 1981 at the Agnes College in Leiden, she started her nursing studies in Voorburg (HBO-V). In 1985 she received her bachelor degree in nursing. From 1985 until 1988 she worked as a registered nurse on several departments of internal medicine in Leiden. In the VU Medical Center, Amsterdam she obtained her Certification for Cardiac Care Nursing in 1989. Subsequently she became an assistant head nurse and worked at several departments of cardiology in the Netherlands. In 2002 she started as a nurse at the section of pharmacology, vascular and metabolic diseases, department of internal medicine, Erasmus MC, Rotterdam. She worked as a vascular clinical nurse at the cardiovascular genetics (CVG) outpatient clinic. From 2005 to 2008 she was president of the Dutch National Society of Cardiovascular Nursing (NVHVV) with 1500 members and board member of the national society committee of the Council of Cardiovascular Nurses and Allied Professions (CCNAP) of the European Society of Cardiology. She was one of the initiators of Continuing Nursing Education (CNE) and contributed to the establishment of the register of quality including an accreditation system for cardiovascular nurses. She was co-auteur of the function profile vascular care and responsible for the recognition of the Cardiac Care program for nurses by the College Ziekenhuis Opleidingen (CZO).

In 2011 she started her Master Advanced Nursing Practice (MANP) en completed this in 2013. Since then she worked as a nurse practitioner spezialised on familial hypercholesterolemia, combining patient care with research in this population. Since 2015 she is the chair of the society of nurse practitioners in the Erasmus MC. She is married to Tjebbe Galema, together they have three sons; Hidde (1994), Jouke (1996) and Geert (1998).

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List of peer reviewed publications

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