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CLINICAL RESEARCH
Coronary artery disease

Patients with familial hypercholesterolaemia are characterized by presence of cardiovascular disease at the time of death

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Aims Untreated familial hypercholesterolaemia (FH) increases the risk of premature atherosclerosis and cardiovascular disease (CVD). This study investigated the presence of CVD in FH patients at the time of death.

Methods and results The presence of CVD, lipid profile, medical treatment, and cause of death was characterized in all deceased Norwegian FH patients, of whom we had access to medical records ($n = 79$, from 1989 to 2010). The mean age at first CVD event was 44 years. The mean age at the time of death was 60 years. Cardiovascular disease was the cause of 50% of the deaths. At the time of death, 93% of the FH patients had established CVD and 69% had experienced myocardial infarction. The FH patients were divided into two groups (cut-off 60 years); FH patients who died at a younger age (mean age 51 years) and at an older age (mean age 71 years). More of the younger FH patients received statins (98 vs. 81%, $P = 0.038$), and fewer received niacin (0 vs. 17%, $P = 0.019$) compared with the older patients. The last measured low-density lipoprotein cholesterol level was higher in the younger patients compared with the older FH patients (5.3 vs. 4.4 mmol/L, $P = 0.033$). There were more current smokers among the younger FH patients compared with the older patients (55 vs. 10%, $P = 0.001$). Interestingly, there were no sex differences in age at the first CVD event or age at the time of death.

Conclusion Cardiovascular disease is present in most FH patients at the time of death, underscoring the severity of FH and the need for early diagnosis and treatment.

Keywords Familial hypercholesterolaemia • Cardiovascular disease • Mortality • Myocardial infarction • Cholesterol • Statins

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Introduction

Heterozygous familial hypercholesterolaemia (FH) is characterized by an accumulation of low-density lipoprotein cholesterol (LDL-C) in the plasma and increased risk of premature cardiovascular disease (CVD) caused by atherosclerosis.[1,2] While the generally accepted estimate for the prevalence of FH is 1/500 globally, recent studies suggest a frequency approaching 1/200.[1,3,4] Despite the fact that FH is the most common inherited metabolic disorder, less than 10% of FH patients are diagnosed and treated worldwide.[1] If left untreated, clinical symptoms of CVD typically manifest in men in their fourth decade and in women in their fifth decade of life.[5] However, the onset of clinically manifested CVD varies widely among patients with FH, even among carriers of an identical mutation.[5–7] A large family-tree mortality study in the Netherlands showed that ~60% of untreated FH patients suffered from premature death, whereas 40% had a normal life expectancy.[8]

Cardiovascular disease is the main cause of death worldwide,[9] and the foremost cause of premature mortality in Europe.[2] However, there are few published studies concerning mortality among FH patients and in deceased heterozygous FH patients.[10–13] Therefore, the aim of the present study was to retrospectively analyse the medical records of deceased FH patients to assess information on the presence of CVD, the age at the time of death, the cause of death, lipid profile, and medical treatment.

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Methods

Approvals

This study was performed in accordance with the Declaration of Helsinki and approved by The Regional Committee of Medical and Health Research Ethics for South-Eastern Norway and by The Norwegian Data Protection Official at Oslo University Hospital.

Study population

In Norway, all molecular diagnosis of FH is performed at the Unit for Cardiac and Cardiovascular Genetics (UCCG) at Oslo University Hospital. From 1992 to 2010, 4688 FH patients were included in the registry, after written informed consent.[14] A total of 113 FH patients died within this time period, representing all registered deaths within the complete cohort of all FH patients with a molecular diagnosis in Norway.[13] Sixty of these 113 deceased FH patients were included in the present study on the basis of access to medical records (*Figure 1*).

The Lipid Clinic at Oslo University Hospital is the major centre for treatment and diagnosis of FH in Norway. Medical records from 30 deceased FH patients from the period 1989–2006 were identified at the Lipid Clinic. Eleven of these patients had a verified genetic mutation for FH and were registered in the UCCG Registry. A mutation had not been confirmed in the remaining FH patients by the time they died. However, by investigating the medical records of living first-degree relatives of the deceased FH patients, a genetic FH mutation was identified in 10 first-degree relatives. The remaining nine FH patients fulfilled the Dutch Lipid Clinic Network criteria for definite FH with a score of eight points or more.[15] The final study group consisted of 79 deceased FH patients.

Data collection

The period of analysis ranged from 1989 (time of death in the first patient) to 2010 (endpoint of data collection).

In Norway, all deaths are reported to the Norwegian Cause of Death Registry (NCoDR) by physicians completing a death certificate.[16,17] The information in the death certificates are coded according to the World Health Organization (WHO) International Classification of Diseases (ICD). From 1989 to 1995, ICD-9 was used, and from 1996 ICD-10 has been used.[16] The coupling of the UCCG Registry and the NCoDR was performed as previously described and included deaths from 1992 to 2010.[13] Fourteen deaths were observed before 1996 and had been coded with ICD-9. These were converted to ICD-10 codes.[18] Cause of death was categorized by the ICD-10 diagnosis coding system; all-cause mortality (all ICD-10 diagnosis codes), CVD mortality (category block I [I00-I99]), cancer mortality (category block C [C00-C97]), and other cause mortality (all ICD-10 diagnosis codes except CVD and cancer). Two observed deaths in the UCCG Registry had main diagnosis code E78.0, pure hypercholesterolaemia, and were classified as CVD deaths.[13] Six deaths occurred between 1989 and 1992 and were therefore not included in the coupling between the UCCG Registry and the NCoDR; these causes of death were based on autopsy reports (two patients) and information in medical records (four patients).

Information on sex, medical history, the presence of CVD, CVD risk factors and comorbidity, the presence of the FH stigmata xanthelasms, xanthomas and corneal arcus, pre-treatment and last measured blood lipid values, and lipid-lowering treatment was obtained from medical records. An overview of the main CVD diagnosis codes used in the study is shown in Supplementary material online, *Table S1*. Owing to insufficient access of coronary revascularization procedures obtainable from the medical records, only information on coronary artery bypass grafting (CABG) surgery was obtained. In cases where LDL-C was not registered, the plasma level of LDL-C was calculated by Friedewald formula.[19] Body mass index (BMI) was calculated as last registered weight (kg) divided by height (m) squared (kg/m^2). Age at first CVD event, age at the time of death, and the duration of lipid-lowering treatment were calculated in whole numbers. Lipid-lowering treatment with statins combined with ezetimibe, resins, fibrates, and/or niacin was considered 'combination treatment'. A reported daily dose of 40 or 80 mg atorvastatin, 80 mg simvastatin or 20 mg rosuvastatin was considered 'potent statin treatment'.

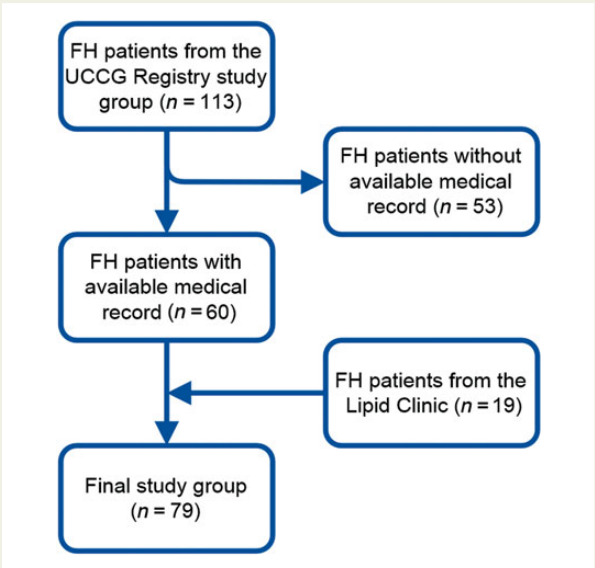

Figure 1 Flow chart showing inclusion of familial hypercholesterolaemia patients in the study group.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, USA). Analysis on differences in characteristics between groups was carried out using independent samples *t*-test with mean and standard deviation (SD) for continuous variables with a normal distribution. In cases of a skewed distribution, Mann–Whitney *U* test with median and interquartile range (IQR), Q1–Q3, was used. Comparison of frequencies between categorical variables was carried out using χ^2 test for independence or Fisher's exact two-tail probability test, and presented in a number of cases and percentages (%). The level of statistical significance was set at $P < 0.05$.

Results

The presence of cardiovascular disease in the familial hypercholesterolaemia patients

Characteristics of the deceased FH patients are shown in *Table 1*. The mean age at the time of death was 60 ± 13.2 years (range 33 to 94 years). Women accounted for 41% of the FH patients. Cardiovascular disease was the cause of death in 50% of the FH patients, followed by cancer (32%, data not shown). Ninety-three per cent of all FH patients had established CVD at the time of death with a mean age of CVD onset at the age of 44 ± 10 years. Coronary heart

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Table 1 Descriptions of all familial hypercholesterolaemia patients

	All FH patients	
		n[a]
Female, *n*(%)	32 (41)	79
Year of death, year	2004 (1998–2007)	79
Age at the time of death, years	60 (13.2)	79
Age at first CVD event, years	44 (10)	45
CVD cause of death, *n*(%)	33 (50)	66
Presence of CVD, *n*(%)		
Overall presence of CVD	71 (93)	76
CHD	61 (86)	71
One or more MIs	43 (69)	62
Atrial fibrillation	9 (19)	48
Heart failure	16 (35)	46
Cerebrovascular disease	12 (25)	49
Diseases of arteries, arterioles and capillaries	21 (39)	54
Aortic aneurysm	8 (15)	54
Lung embolus or deep vein thrombosis	7 (14)	50
FH stigmata, *n*(%)		
Xanthelasms	22 (31)	72
Xanthomas	41 (57)	72
Corneal arcus	24 (62)	39
CVD risk factors and comorbidity		
Smoker (both pre and active), *n*(%)	31 (61)	51
Smoker (active), *n*(%)	19 (37)	51
Hypertension, *n*(%)	32 (46)	69
Diabetes mellitus, *n*(%)	12 (22)	54
BMI, kg/m^2	27.0 (23.4–29.8)	37
Cancer, *n*(%)	28 (52)	54
Rheumatologic disease, *n*(%)	7 (15)	48
Lipid-lowering treatment and *n*-3 supplements		
Statins or combination treatment, *n*(%)	67 (91)	74
Total years of statin treatment, years	8 (3–12)	29
Potent statin type, *n*(%)	33 (54)	61
Resins, *n*(%)	17 (27)	62
Niacin, *n*(%)	4 (7)	62
Ezetimibe, *n*(%)	13 (21)	62
LDL-C-/plasmapheresis, *n*(%)	5 (7)	74
n-3 supplements, *n*(%)	14 (24)	59
Laboratory parameters		
Pre-treatment, mmol/L		
TC	12.3 (2.9)	72
LDL-C	9.6 (2.4)	46
HDL-C	1.2 (0.4)	47
TG	1.72 (1.20–2.77)	50

Continued

Table 1 *Continued*

	All FH patients	
		n[a]
Last registered, mmol/L		
TC	6.9 (1.8)	63
LDL-C	5.0 (1.8)	57
HDL-C	1.3 (0.5)	61
TG	1.39 (1.00–2.01)	62
Lp(a), mg/L	277 (130–517)	29
Coronary revascularization procedures		
One or more CABGs, *n*(%)	18 (29)	63

Data are given as mean(SD), median(IQR) or *n*(%).
CVD, cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; Lp(a), lipoprotein(a); CABG, coronary artery bypass graft.
[a]*n* indicates number of individuals.

disease (CHD) was present in 86% of the FH patients and 69% of the FH patients had experienced one or more myocardial infarction (MI) at the time of death. Prevalence of atrial fibrillation was 19% and 39% of the FH patients had other vascular diseases. Xanthelasms, xanthomas, and corneal arcus were present in 31, 57, and 62% of the FH patients, respectively. Hypertension was present in almost 50% of the FH patients, and 22% had diabetes mellitus (DM). Ninety-one per cent received statins or combination treatment. The mean duration of statin treatment was 8 years. Pre-treatment total cholesterol (TC) and LDL-C was 12.3 $\pm$ 2.9 and 9.6 $\pm$ 2.4 mmol/L, respectively. The last measured TC and LDL-C level before death was 6.9 $\pm$ 1.8 and 5.0 $\pm$ 1.8 mmol/L, respectively. Twenty-nine per cent of the FH patients had had one or more CABG.

Younger vs. older age at the time of death

In a recent study including all registered deaths within the complete FH cohort in Norway during 1992–2010, the average age at the time of death was approximately 60 years,[13] as was the case in the present study. Therefore, patients were divided into two groups with a cut-off of 60 years (*Table 2*). As shown in *Figure 2*, whereas 55% of the patients who died at a younger age (mean age at the time of death 51 years) were active smokers, only 10% of the patients who died at an older age (mean age at the time of death 71 years) were active smokers ($P = 0.001$). Ninety-eight per cent of the younger and 81% of the older FH patients received statins or combination treatment (*Figure 3*, $P = 0.038$). None of the patients who died at a younger age received niacin compared with 17% of the patients who died at an older age ($P = 0.019$). The last measured mean level of LDL-C was significantly higher among the younger FH patients compared with that of the older patients (*Figure 4*, 5.3 $\pm$ 2.0 vs. 4.4 $\pm$ 1.3 mmol/L, $P = 0.033$). There were no differences between the groups in the presence of CVD at the time of death.

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Table 2 Demographics of familial hypercholesterolaemia patients divided by mean age at time of death and of female vs. male familial hypercholesterolaemia patients

	Age at the time of death				P	Sex				P
	Younger (<60 years)		Older (>60 years)			Female		Male		
		n[a]		n			n		n	
Female, n(%)	20 (46)	44	12 (34)	35	0.44					
Year of death, (year)	2004 (1998–2007)	44	2004 (1997–2008)	35	0.67	2004 (1998–2007)	32	2004 (1998–2008)	47	0.46
Age at the time of death, (years)	50 (8.5)	44	71 (7.8)	35	–	59 (15.3)	32	60 (11.6)	47	0.72
Age at first CVD event, (years)	40 (8.9)	27	50 (8.4)	18	<0.001	46 (8.9)	16	43 (10.7)	29	0.32
CVD cause of death, n(%)	20 (57)	35	13 (49)	31	0.32	11 (42)	26	22 (55)	40	0.45

Data are given as mean(SD), median(IQR) or n(%).
CVD, cardiovascular disease.
[a]n indicates number of individuals.

The presence of cardiovascular disease in female vs. male familial hypercholesterolaemia patients

The presence of CVD was evaluated according to sex (*Figure 5*). Fewer female FH patients had CVD at the time of death compared with male FH patients (84 vs. 100%, $P = 0.011$). No other statistical significant differences between female and male FH patients were observed; neither in mean age at the time of death, in age at the first CVD event, nor in the presence of CHD (*Table 2*).

Cardiovascular disease risk factors and lipid values in female vs. male familial hypercholesterolaemia patients

A greater number of female FH patients had rheumatologic disease (32 vs. 3%, $P = 0.011$) and significantly fewer females had hypertension (36 vs. 54%, $P = 0.022$) at the time of death compared with male FH patients (see Supplementary material online, *Table S2*). Females had lower level of pre-treatment triglycerides [1.40 (0.97–2.35) vs. 2.09 (1.63–3.60) mmol/L, $P = 0.018$] and higher last measured high-density lipoprotein cholesterol (HDL-C) level compared with males (1.5 ± 0.3 mmol/L vs. 1.2 ± 0.4 mmol/L, $P = 0.007$). There were no differences between sexes in any of the other biochemical and clinical parameters.

Discussion

The present study shows that most FH patients had established CVD at the time of death. In the death certificates, CVD was recorded as the main cause of death in 50% of the FH patients, while at the same time 93% of the FH patients suffered from CVD at the time of death, indicating that the main cause of death underestimates the true presence of CVD in FH patients. Clearly, CVD was a major issue for many FH patients as 69% had experienced one or more MIs at the time of death.

A prospective study of 345 FH patients by Mohrschladt *et al.*[12] showed that male FH patients treated with statins from middle age (age 40–59 years) remained at an increased risk for CVD, especially if they had had a CVD event before statin treatment was initiated. Most of the FH patients in our study had experienced one or more CVD events before statins were initiated. This suggests that the FH diagnosis was set after the first CVD event, underscoring that FH is severely underdiagnosed in the population.[1] A recent study by Nanchen *et al.* [20] showed that a phenotypic diagnosis of possible FH was present in 54.1% of 1451 patients hospitalized with premature acute coronary syndromes.

The FH patients in this study received statins for an average of 8 years prior to death. However, only 54% of the FH patients, with a highly premature mean age of 44 years at the first CVD event, received a potent statin type (bearing in mind that some patients died in the 1990s, at a time with less aggressive treatment goals). Inadequate dose and late introduction of lipid-lowering treatment probably lead to a higher risk of CVD death, as shown in studies on patients without FH.[21] Versmissen *et al.* [22] showed a CVD risk reduction of 76% in FH patients on statins vs. untreated patients during a mean follow-up of 8.5 years. The overall CVD risk of the

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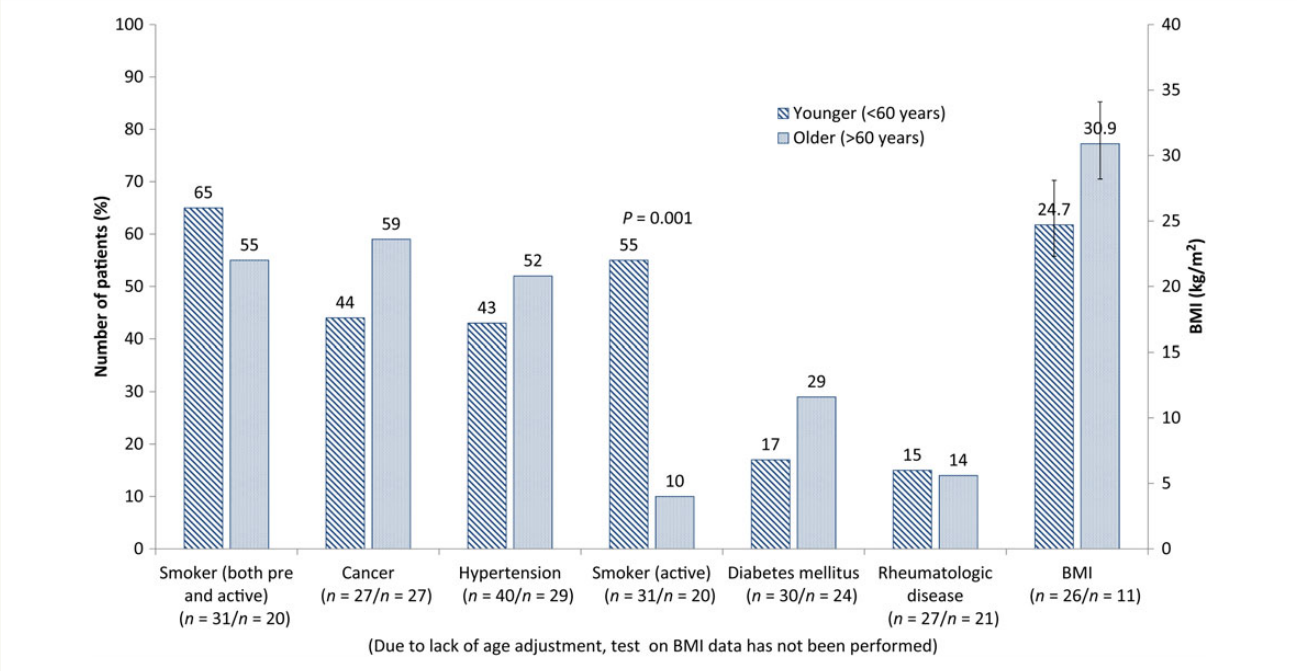

Figure 2 Cardiovascular disease risk factors and comorbidity in familial hypercholesterolaemia patients divided into two groups based upon the mean age at the time of death; younger (<60 years) and older (>60 years). Bars represent number of patients (%). For body mass index, bars represent median (inter-quartile range). Shaded bars indicate younger and blue bars indicate older familial hypercholesterolaemia patients. Numbers of patients are indicated at each bar.

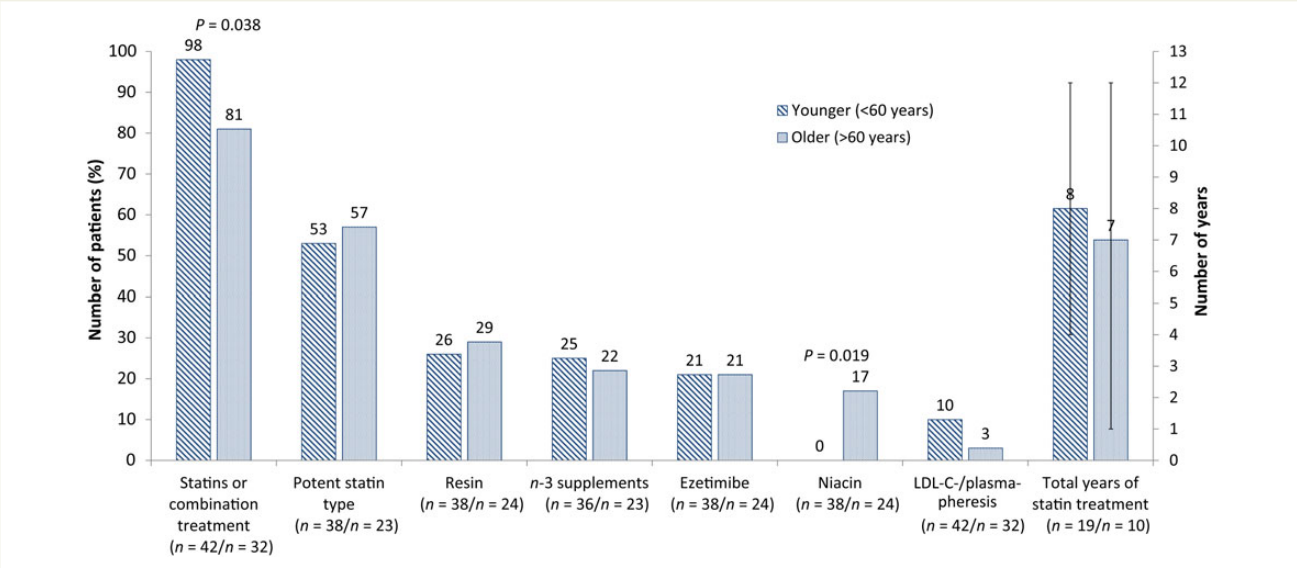

Figure 3 Lipid-lowering treatment in familial hypercholesterolaemia patients divided into two groups based upon the mean age at the time of death; younger (<60 years) and older (>60 years). Bars represent number of patients (%). For total years of statin treatment, bars represent median (inter-quartile range). Shaded bars indicate younger and blue bars indicate older familial hypercholesterolaemia patients. Numbers of patients are indicated at each bar.

FH patients who reached LDL-C level of 4.0 mmol/L was almost similar to that of the general Dutch population adjusted for age and sex, indicating that long-term statin therapy in CVD-free FH patients is effective, even with LDL-C levels above the recommended goal.[22] However, in non-statin-treated FH patients, the risk of CVD is increased 13-fold compared with FH

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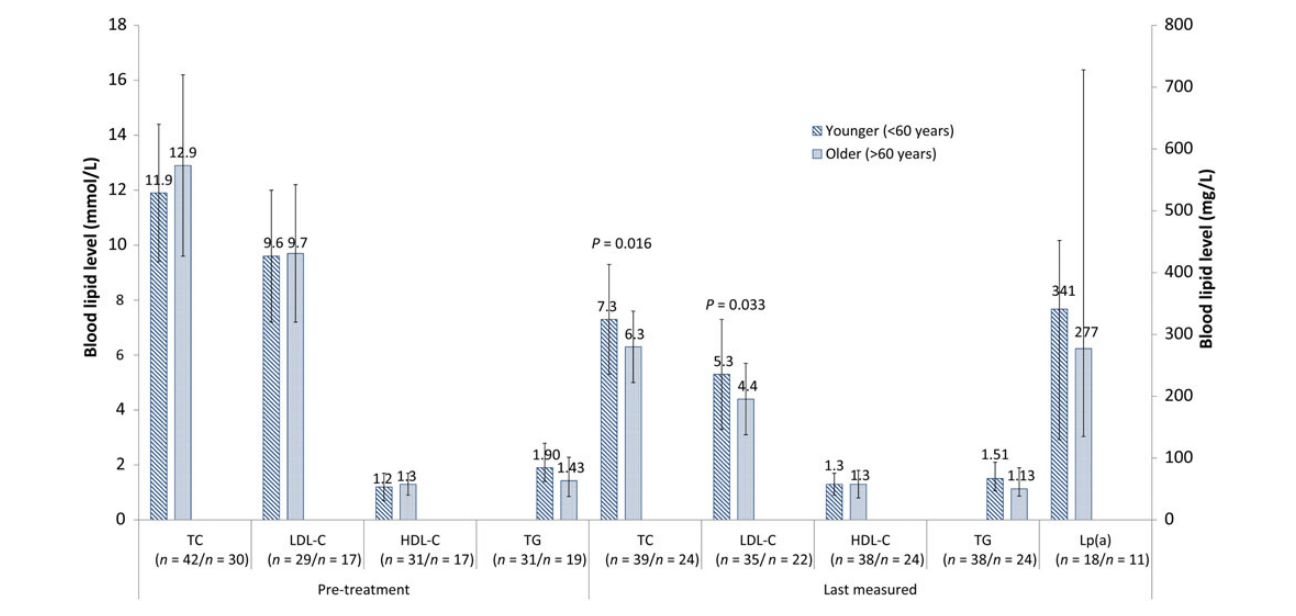

Figure 4 Blood lipid values in familial hypercholesterolaemia patients divided into two groups based on the mean age at the time of death; younger (<60 years) and older (>60 years). Bars represent mean ± SD. For triglycerides and lipoprotein(a), bars represent median (interquartile range). Shaded bars indicate younger and blue bars indicate older familial hypercholesterolaemia patients. Numbers of patients are indicated at each bar.

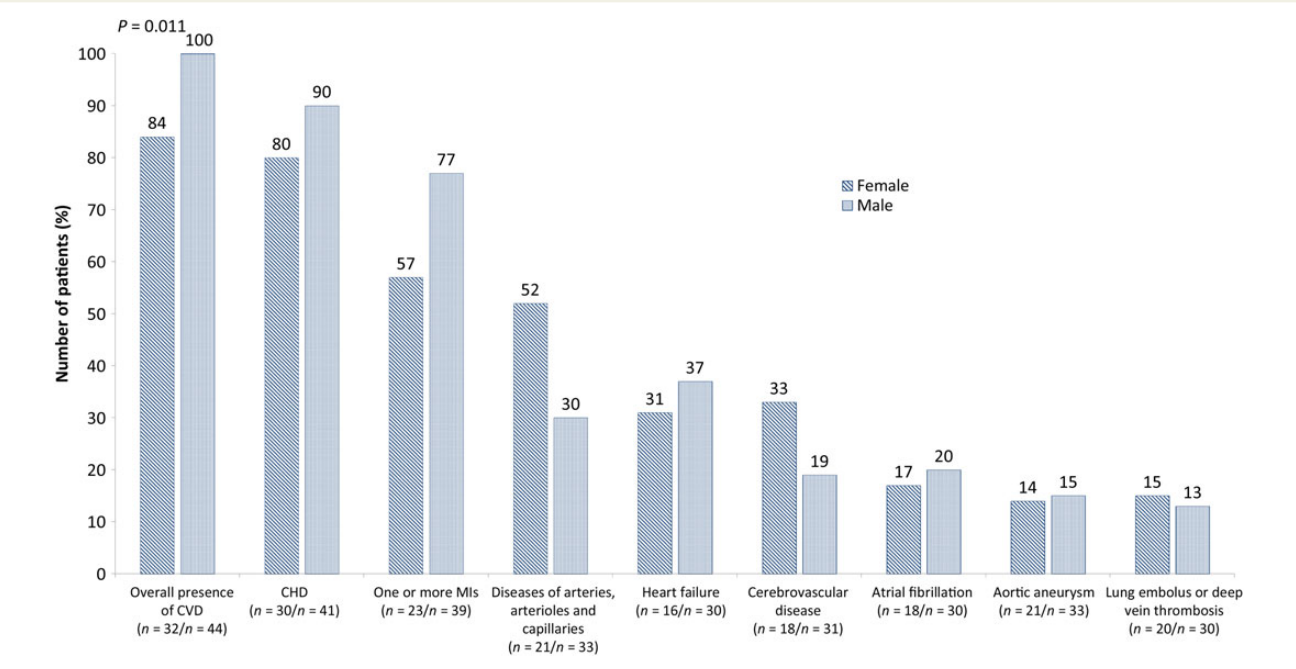

Figure 5 The presence of cardiovascular disease in female vs. male familial hypercholesterolaemia patients. Bars represent number of patients (%). Shaded bars indicate female and blue bars indicate male familial hypercholesterolaemia patients. Numbers of patients are indicated at each bar.

patients receiving statins.[3] In this study, many patients died young after having experienced one or more premature CHD events such as MI.

Cardiovascular disease deaths accounts for 46% of all deaths in Europe[23] and accounted for 37% of all deaths in the Norwegian population in 2010,[13] compared with 50% of the deaths in this FH

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cohort. Even though the prevalence of CVD deaths in the FH patients is not very different from the general population, in recent findings from Mundal *et al.*[13] the FH patients had a significantly lower mean age at the time of CVD death. Data suggest that statins may lower risk of MI in FH patients to the same level as the general population.[22] However, both the present study and Mundal's study were carried out in the 'statin era', and despite statin treatment age at the time of death was still lower in the deceased FH patients than in the general population.[13] Although more of the FH patients who died at a younger age received statins when compared with the older FH patients, their last measured level of TC and LDL-C was significantly higher than in the older patients. The present study underscores the vital clinical importance of optimal follow-up of young FH patients in order to secure a good compliance of medication use and to optimize the treatment once given to reach recommended lipid-lowering treatment targets. We have previously shown that despite long-term lipid-lowering therapy in FH patients and normalization of lipid levels, there still was an inflammatory imbalance in these patients potentially contributing to premature disease, supporting the present findings.[24]

It has been estimated that by the age of 65 years, ~50% of women and 85% of men with FH have experienced a coronary event if not appropriately treated.[6] The present study suggests that the numbers are even higher since 80% of the women and 90% of the men who died of any cause had established CHD at a death age of 59 and 60 years, respectively. The mean age at the time of CVD deaths was 57 years in both sexes. One might hypothesize that life-long exposure to high LDL-C may be so detrimental that it counterbalances the positive effect of sex on CVD usually seen among non-familial hypercholesterolaemic persons. Also, pregnancy and lactation leads to the disadvantage of fewer effective years of treatment in women. The present data underlines the importance of treating both sexes equally efficient in FH.

Active smoking and high on-treatment LDL-C levels characterized FH patients who died prematurely compared with those who died later. This is consistent with previous findings.[25] The presence of DM was very high among the deceased FH patients (22%) and much higher than that of the age-adjusted rate in the general population. However, the rate of DM in the present study must not be considered representative of the rate in the general FH population since this high rate was observed in the FH patients who died. The most conceivable interpretation of this finding is therefore that DM represents a major risk factor for death in FH patients.

Twenty-nine per cent of the deceased FH patients had had one or more CABGs. The relatively high number of CABGs underscores the severity of the disease, but must also be considered in the context of the time of which the data were collected. The prevalence of atrial fibrillation among the deceased FH patients aged 60 years was approximately at the same level as in those aged 85 years or older in the general population (17.8%),[26] reflecting the massive burden of CVD in the FH population. Fifteen per cent of the FH patients in our study had aortic aneurysm when compared with 2.2% in women and 8.9% in men in the general Norwegian population.[27] Aortic aneurysm is two to six times more prevalent in males than in females; however, there was no difference between sexes in this study.

An important strength in our study was that the majority of all FH patients in the study population had a verified genetic mutation for FH. Furthermore, the coupling of the UCCG Registry to the NCoDR allowed us to categorize the main cause of death in all the FH patients. Few, if any, other studies have investigated the medical history and the presence of CVD in such a high number of deceased FH patients.

Some care, however, is needed in interpreting our findings. The selection and inclusion of FH patients was based on the time of death (1989–2010). Still, the patients were not a random sample of the total Norwegian FH population. Most patients were followed up at the Lipid Clinic with an experienced staff. Reflecting the time frame the collected data from the medical records represents, all values were not available for all FH patients. For the same reason, detailed information on the presence of CVD such as different types of MIs was scarce and we did not have available information on coronary revascularization procedures or other invasive methods. Another study limitation was that the FH population was about 4.8 years younger when compared with the Norwegian population.[13] Ideally, when comparing the mean age for CVD deaths in these two cohorts, similar mean age in the two populations should have been present.

In conclusion, our results show that over 90% of FH patients were characterized by the presence of CVD at the time of death. The FH patients died at a highly premature age of 60 years. Three out of four FH patients had experienced one or more MIs prior to death. Classical risk factors were more prevalent in FH patients who died at a younger age. The present study clearly emphasizes the severity of carrying an FH mutation and the urgent need for early diagnosis and treatment for these patients, including young women.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: During the past 5 years K.R. has received honoraria for lectures or expert meetings from Merck, Pfizer, Mills DA, Melk.no, Apotek1, Pronova, Amgen, Genzyme, and Sanofi; none of which are related to the contents of this manuscript. During the past 5 years K.B.H. has received research grants or honoraria from Tine, Mills, and Olympic Seafood, and Amgen; none of which are related to the contents of this manuscript.

References

1. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Boren J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013;**34**:3478–3490. a.
2. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R,

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Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;**32**:1769–1818.

3. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J Clin Endocrinol Metab* 2012;**97**:3956–3964.
4. Sjouke B, Kusters DM, Kindt I, Besseling J, Defesche JC, Sijbrands EJ, Roeters van Lennep JE, Stalenhoef AF, Wiegman A, de Graaf J, Fouchier SW, Kastelein JJ, Hovingh GK. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. *Eur Heart J* 2015;**36**:560–565.
5. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* 1991;**303**: 893–896.
6. Civeira F, International Panel on Management of Familial Hypercholesterolemia. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004;**173**:55–68.
7. Jansen AC, van Wissen S, Defesche JC, Kastelein JJ. Phenotypic variability in familial hypercholesterolaemia: an update. *Curr Opin Lipidol* 2002;**13**:165–171.
8. Sijbrands EJ, Westendorp RG, Defesche JC, de Meier PH, Smelt AH, Kastelein JJ, Kaprio J. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. *BMJ* 2001;**322**:1019–1023.
9. World Health Organization. Cardiovascular diseases (CVDs). **http://www.who.int/mediacentre/factsheets/fs317/en/index.html (20 October 2014)**.
10. Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P, Seed M, Humphries SE. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur Heart J* 2008;**29**:2625–2633.
11. Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. *Atherosclerosis* 1999;**142**:105–112.
12. Mohrschladt MF, Westendorp RG, Gevers Leuven JA, Smelt AH. Cardiovascular disease and mortality in statin-treated patients with familial hypercholesterolemia. *Atherosclerosis* 2004;**172**:329–335.
13. Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierod MB, Leren TP, Retterstol K. Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992–2010. *J Am Heart Assoc* 2013;**3**:e001236.
14. Leren TP, Berge KE. Subjects with molecularly defined familial hypercholesterolemia or familial defective apoB-100 are not being adequately treated. *PLoS One* 2011;**6**:e16721.
15. World Health Organization. *Familial Hypercholesterolemia; Report of a Second WHO Consultation*. WHO ed. Geneva: WHO; 1999.
16. Gjertsen F. [Cause of death registry--an important data source for medical research]. *Tidsskr Nor Laegeforen* 2002;**122**:2551–2554.
17. Norwegian Institute of Public Health. The Norwegian Cause of Death Registry 1951–2014. **http://statistikkbank.fhi.no/dar/ (26 October 2014)**.
18. World Health Organization. *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. **http://www.who.int/classifications/icd/icdonlineversions/en/ (22 August 2014).**
19. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;**18**:499–502.
20. Nanchen D, Gencer B, Auer R, Räber L, Stefanini GG, Klingenberg R, Schmied CM, Cornuz J, Muller O, Vogt P, Jüni P, Matter CM, Windecker S, Lüscher TF, Mach F, Rodondi N. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. *Eur Heart J* 2015;**21**:2438–2445.
21. Delahoy PJ, Magliano DJ, Webb K, Grobler M, Liew D. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. *Clin Ther* 2009;**31**:236–244.
22. Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, Heeringa J, Witteman JC, Lansberg PJ, Kastelein JJ, Sijbrands EJ. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008;**337**:a2423.
23. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J* 2014;**35**:2929.
24. Holven KB, Narverud I, Lindvig HW, Halvorsen B, Langslet G, Nenseter MS, Ulven SM, Ose L, Aukrust P, Retterstol K. Subjects with familial hypercholesterolemia are characterized by an inflammatory phenotype despite long-term intensive cholesterol lowering treatment. *Atherosclerosis* 2014;**233**:561–567.
25. Jansen AC, van Aalst-Cohen ES, Tanck MW, Trip MD, Lansberg PJ, Liem AH, van Lennep HW, Sijbrands EJ, Kastelein JJ. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: data in 2400 patients. *J Intern Med* 2004;**256**:482–490.
26. The European Society of Cardiology. *ESC Pocket Guidelines. Management of Patients with Atrial fibrillation*. Sophia Antipolis: The European Society of Cardiology; 2012, 47.
27. Singh K, Bonaa KH, Jacobsen BK, Bjork L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study : The Tromso Study. *Am J Epidemiol* 2001;**154**:236–244.

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