ORIGINAL RESEARCH

Mortality Among Patients With Familial Hypercholesterolemia: A Registry-Based Study in Norway, 1992–2010

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***Background*—**Untreated patients with familial hypercholesterolemia are at increased risk of premature cardiovascular death. The primary aim of this study was to investigate whether this is also the case in the statin era.

***Methods and Results*—**In this registry-based study, 4688 male and female patients from the Unit for Cardiac and Cardiovascular Genetics (UCCG) Registry with verified molecular genetic diagnosis of familial hypercholesterolemia in the period 1992–2010 were linked to the Norwegian Cause of Death Registry. Standardized mortality ratios and 95% CIs were estimated. There were 113 deaths. Mean age of death was 61.1 years. Cardiovascular disease was the most common cause of death (46.0%), followed by cancer (30.1%). Compared with the Norwegian population, cardiovascular disease mortality was significantly higher in the UCCG Registry in all age groups younger than 70 years (standardized mortality ratio 2.29, 95% CI 1.65 to 3.19 in men and women combined; standardized mortality ratio 2.00, 95% CI 1.32 to 3.04 in men; standardized mortality ratio 3.03, 95% CI 1.76 to 5.21 in women). No significant differences were found in all-cause mortality or cancer mortality.

***Conclusions*—**Despite prescription of lipid-lowering drugs, familial hypercholesterolemia patients still had significantly increased cardiovascular disease mortality compared with the general Norwegian population. **(*J Am Heart Assoc*. 2014;3:e001236 doi: 10.1161/JAHA.114.001236)**

Key Words: cardiovascular diseases • hypercholesterolemia • mortality • registries • statins

Familial hypercholesterolemia (FH) is an autosomal dominant disorder usually caused by mutations in the low-density lipoprotein (LDL) receptor gene. Untreated FH results in an accumulation of LDL cholesterol, which can lead to atherosclerosis and an increased risk of premature cardiovascular disease (CVD).[1–3]

Worldwide, >10 million people have FH, of which ≈200 000 persons die of CVD each year.[4,5] In the Norwegian population, the estimated prevalence of heterozygous FH is ≈1 in 300 and ≈1 in 500 globally.[6,7] Approximately 50% of untreated men and women with heterozygous FH will develop CVD before 50 and 60 years of age, respectively.[8] About 5% of the patients suffering a myocardial infarction before the age of 60 years have heterozygous FH.[9] Given that the prevalence of FH is ≈0.2% worldwide, this suggests an almost 25-fold increase in the risk of myocardial infarction at an age younger than 60 years.

The varying risk of death among FH patients suggests an interaction between genetic and environmental factors.[10] There are few published studies of mortality in treated heterozygous FH patients.[3,11] Reductions in all-cause mortality, cancer, and coronary mortality have been observed in statin-treated FH patients.[3,11] For ethical reasons, randomized placebo-controlled studies of mortality and other hard end points cannot be conducted among patients with FH. Consequently, treatment of FH patients is based largely on a few published observational studies and results of clinical trials of lipid-lowering drugs conducted in patients with other forms of hypercholesterolemia.[11]

In Norway, all molecular genetic diagnosis of FH is performed at the Unit for Cardiac and Cardiovascular Genetics (UCCG) at Oslo University Hospital. All diagnosed FH patients are included in the UCCG Registry after providing written informed consent. Approximately 200 different mutations in the LDL receptor gene have been found to cause FH among patients living in Norway, and 4 mutations are responsible for 47.2% of all FH cases.[4]

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The aim of this study was to investigate the mortality and cause of death among all patients diagnosed with FH in Norway by linking data from the UCCG Registry and the Norwegian Cause of Death Registry. We especially examined CVD mortality among FH patients in relation to age and sex. This is the largest cohort study with verified molecular genetically diagnosed heterozygote FH patients.

Methods

Approvals

The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics and the Norwegian Data Protection Official at Oslo University Hospital.

Study Design

This was a registry-based study of a cohort with up to 19 years of follow-up (1992–2010).

Registries

Study data was derived from the UCCG Registry and the Norwegian Cause of Death Registry. Statistics Norway was responsible for linking the 2 registries. The UCCG Registry consisted of 4688 patients with verified molecular genetic diagnosis of FH diagnosed in the period from 1992 to 2010. In the same period, the Norwegian Cause of Death Registry included 823 626 deaths.

Molecular genetic testing for FH has been performed in Norway since 1992 when the UCCG Registry at Oslo University Hospital, Rikshospitalet was established. Patients with verified FH are recommended lipid-lowering treatment according to existing national guidelines based on the European Society of Cardiology guidelines.

The Norwegian Cause of Death Registry has been available since 1951.[12] Physicians are required to complete a death certificate of all reported deaths collected by this registry. The coding system used in the death certificates is the International Classification of Diseases (ICD).[12,13] From 1992 to 1995, the ninth revision (ICD-9) was used, and since 1996, the 10th revision (ICD-10) has been used.

Since 2005, the Norwegian Cause of Death Registry has used the computer program Automatic Classification of Medical Entities (ACME), developed by US National Center for Health Statistics, to identify and secure the correct underlying cause of death according to rules and guidelines established by the World Health Organization (ICD).[14]

The Norwegian Cause of Death Registry has been validated both internal and externally. In 2011, a Norwegian autopsy study, "Diagnostic Validity of Fatal Cerebral Strokes and Coronary Deaths in Mortality Statistics," was published and showed substantial agreement between mortality statistics and autopsy findings for both fatal strokes and coronary deaths in the period from 1965 to 2005 in Norway.[15]

Data Collection

Data collection and the period of analysis were limited to 1992–2010 based on when molecular genetic testing for FH was initiated. Variables from the UCCG Registry were date of inclusion in the registry, sex, age, type of mutation, and other demographic data. Hospital records were used to extract data on coexisting diseases, clinical signs, use of lipid-lowering drugs, and laboratory parameters as lipid profiles. All data extracted from hospital records were limited to those who died. The linkage to the Norwegian Cause of Death Registry gave data on main death diagnosis and date of death.

Deaths were categorized as follows: all-cause mortality (all ICD-10 codes), CVD mortality (category block I in the main ICD-10 diagnosis codes), cancer mortality (category block C in the main ICD-10 diagnosis codes), and other-cause mortality (all ICD-10 codes except cancer and CVD). Only 3 deaths were observed before 1996 (ie, coded with ICD-9), and these were converted to ICD-10 codes.[13] Five observed deaths in the UCCG Registry had a main diagnosis of pure hypercholesterolemia (E78.0). Because it is not possible to die of pure hypercholesterolemia, these patients likely suffered from CVD and thus were classified as CVD deaths. Data on the exact inclusion date of the first 704 patients in the UCCG Registry were not available. Because we know that all of these patients were included in the UCCG Registry in the period 1992–1995, their inclusion year was defined as 1992.

Statistical Analysis

The mortality in the UCCG Registry was compared with the mortality in the general Norwegian population according to sex, birth year, and calendar year. The analysis was performed using SPSS version 19.0 (IBM Corp) and Excel 2010 (Microsoft).

All estimations were based on time of patient inclusion in the UCCG Registry and the cohort to the time point the patient reached the study end point, which was defined as year of death or end of study (ie, December 31, 2010). Age at death was calculated in whole numbers, without decimal notations at the end of the actual year of death.

Age was calculated by subtracting year of birth from the calendar year. Follow-up time was calculated according to sex, calendar year, and year of birth.

Table 1. Selected Characteristics of the 113 Observed Deaths in the Unit for Cardiac and Cardiovascular Genetics Registry

Variables	Total (n=113)	Men (n=59)	Women (n=54)
Age at inclusion, y	54.8 (12.2 to 92.4)	52.5 (12.2 to 81.1)	57.4 (29.0 to 92.4)
Age at death, y			
Total	61.1 (18 to 94)	58.1 (18 to 85)	64.4 (31 to 94)
CVD	62.2 (33 to 91)	57.2 (33 to 80)	67.2 (33 to 91)
Cancer	63.4 (37 to 85)	68.3 (52 to 85)	57.8 (37 to 83)
Duration of follow-up (y)	6.3 (0 to 18.9)	5.6 (0 to 18.6)	7.0 (0 to 18.9)

Values are given as mean (range). CVD indicates cardiovascular disease.

The age- and calendar-specific mortality rates for men and women in the Norwegian population were calculated by Statistics Norway. Statistics Norway also estimated the expected numbers of deaths and standardized mortality ratios (SMRs).[11,16] Both total and separate calculations were made for each sex and were performed for all-cause mortality, CVD mortality, cancer mortality, and death by other causes.

The results were reported as SMRs with corresponding 95% CIs. SMRs were calculated by indirect standardization and derived from the ratio of the number of observed deaths (D_p) to the number of expected deaths (E_p) in the patient population: $SMR=D_p/E_p$.[16,17] The 95% CIs for SMR were calculated as follows:[16–18]

$$\left(e^{-1.96/\sqrt{D_p}} \cdot SMR,\ e^{1.96/\sqrt{D_p}} \cdot SMR\right).$$

The number of expected deaths in the patient population (E_p) was estimated by use of the formula below. All calculations were based on equal mortality, as in the general Norwegian population, and were estimated by adding total time spent in the cohort (in the patient population) for every birth and calendar year multiplied by the mortality rate for men and women in the general Norwegian population from 1992 to 2010 for all corresponding x and y values:[16,18]

$$E_p = \sum_{y=1992}^{2010} \sum_{x=1913}^{2010} M_p(x,y) \cdot R(x,y).$$

Total time spent by the patient population during calendar year y for patients born in year x was given as M_p (x, y).The mean population in year y for the population born in year x was given as follows: $M(x, y)=½ (L(x, y)+L(x, y+1))$. $L(x, y)$ defined the Norwegian population on January 1 of year y that were born in year x. The mortality rate of the Norwegian population born in year x for year y was given as follows: $R(x, y)=D(x, y)/M(x, y)$. $D(x, y)$ was defined as the number of observed deaths for the Norwegian population born in year x in year y.[16,18]

Results

The FH Study Sample

The UCCG Registry consisted of 4688 patients, 2238 men and 2450 women. Mean follow-up was 8 years (range 0 to 19 years). All of these patients were heterozygote except 10 who were homozygote. Mean age at inclusion in the UCCG Registry was 33.6 years (range 0 to 92.4 years): 32.0 years for men and 35.0 years for women. Mean age for both sexes at the study end point was 41.6 years (range 0.3 to 94.7 years).

A total of 113 deaths were observed during follow-up, of which all were heterozygote. The characteristics of the 113 deaths are summarized in Table 1. CVD mortality was most common (52 patients, 46.0%), followed by cancer mortality (34 patients, 30.1%), and mortality by other causes (27 patients, 23.9%). Age at inclusion, age at death, and time of follow-up are summarized in Table 1.

Among the deaths were 32 different mutation types (Table 2). The most common mutations were in the LDL

Table 2. Mutation Type Among the 113 Observed Deaths

Mutation Type	Both Sexes	Men	Women
313+1, G>A	33 (29.2)	19 (32.2)	14 (25.6)
C210G	12 (10.6)	5 (8.5)	7 (13.0)
R3500Q	7 (6.2)	2 (3.4)	5 (9.2)
S78X	7 (6.2)	3 (5.1)	4 (7.4)
D200N	6 (5.3)	5 (8.5)	1 (1.8)
W23X	6 (5.3)	2 (3.4)	4 (7.4)
N804K	5 (4.4)	4 (6.8)	1 (1.8)
R395W	5 (4.4)	2 (3.4)	3 (5.5)
P664L	5 (4.4)	1 (1.7)	4 (7.4)
Other*	27 (23.9)	16 (27.1)	11 (20.4)
Total	113 (100)	59 (100)	54 (100)

Values are given as number (%). All mutations are in the LDL receptor gene except for mutation R3500Q, which is in the apolipoprotein B gene.
*Pooled data of 32 mutation types occurring with a frequency <2%.

Table 3. All-Cause Mortality in the Unit for Cardiac and Cardiovascular Genetics Registry

Attained Age (y)	Observed Deaths	Expected Deaths	SMR	95% CI
Both sexes				
0 to 19	2	1.66	1.21	0.30 to 4.83
20 to 39	11	9.00	1.22	0.68 to 2.21
40 to 59	34	33.05	1.03	0.73 to 1.44
60 to 69	29	33.14	0.88	0.61 to 1.26
70 to 79	20	33.29	0.60*	0.39 to 0.93
>80	17	19.85	0.86	0.53 to 1.38
Total	113	130.01	0.87	0.72 to 1.05
0 to 69	76	76.88	0.99	0.79 to 1.24
Men				
0 to 19	2	1.12	1.78	0.45 to 7.13
20 to 39	6	6.11	0.98	0.44 to 2.19
40 to 59	17	19.25	0.88	0.55 to 1.42
60 to 69	20	19.54	1.02	0.66 to 1.59
70 to 79	7	17.01	0.41*	0.20 to 0.86
>80	7	5.52	1.27	0.60 to 2.66
Total	59	68.58	0.86	0.67 to 1.11
0 to 69	45	46.05	0.98	0.73 to 1.31
Women				
0 to 19	0	0.53	0	—
20 to 39	5	2.89	1.73	0.72 to 4.15
40 to 59	17	13.80	1.23	0.77 to 1.98
60 to 69	9	13.60	0.66	0.34 to 1.27
70 to 79	13	16.28	0.80	0.46 to 1.38
>80	10	14.33	0.70	0.38 to 1.30
Total	54	61.44	0.88	0.67 to 1.15
0 to 69	31	30.83	1.01	0.71 to 1.43

SMR indicates standardized mortality ratio.
*$P<0.05$.

Table 4. Cardiovascular Disease Mortality in the Unit for Cardiac and Cardiovascular Genetics Registry

Attained Age (y)	Observed Deaths	Expected Deaths	SMR	95% CI
Both sexes				
0 to 19	0	0.06	—	—
20 to 39	5	0.62	8.03*	3.34 to 19.28
40 to 59	16	6.43	2.49*	1.52 to 4.06
60 to 69	14	8.15	1.72*	1.02 to 2.90
70 to 79	11	10.19	1.08	0.60 to 1.95
>80	6	7.87	0.76	0.34 to 1.70
Total	52	33.33	1.56*	1.19 to 2.05
0 to 69	35	15.27	2.29*	1.65 to 3.19
Men				
0 to 19	0	0.03		
20 to 39	3	0.44	6.85*	2.21 to 21.24
40 to 59	9	4.75	1.89	0.99 to 3.64
60 to 69	10	5.74	1.74	0.94 to 3.24
60 to 79	3	5.49	0.55	0.18 to 1.70
>80	1	2.04	0.49	0.07 to 3.49
Total	26	18.50	1.41	0.96 to 2.06
0 to 69	22	10.98	2.00*	1.32 to 3.04
Women				
0 to 19	0	0.03		
20 to 39	2	0.19	10.81*	2.70 to 43.23
40 to 59	7	1.68	4.17*	1.99 to 8.75
60 to 69	4	2.41	1.66	0.62 to 4.43
70 to 79	8	4.70	1.70	0.85 to 3.40
>80	5	5.83	0.86	0.36 to 2.06
Total	26	14.83	1.75*	1.19 to 2.58
0 to 69	13	4.30	3.03*	1.76 to 5.21

SMR indicates standardized mortality ratio.
*$P<0.05$.

receptor gene; however, 7 patients had mutation R3500Q in the apolipoprotein B gene.

The mortality results are presented in Tables 3 through 6. There was no significant difference in all-cause mortality between the UCCG Registry and the general population except a significant reduced SMR at age group 70 to 79 years (Table 3). CVD mortality was significantly higher in the UCCG Registry compared with the Norwegian population in all age groups younger than 70 years (SMR 2.29, 95% CI 1.65 to 3.19 in men and women combined; SMR 2.00, 95% CI 1.32 to 3.04 in men; SMR 3.03, 95% CI 1.76 to 5.21 in women) (Table 4). No significant differences were found for cancer mortality (Table 5). For death by other causes, there were significantly reduced SMRs in both sexes combined and in men (Table 6). Data on lipid-lowering treatment were available in 68 of the 113 dead patients. Sixty patients (35 men, 25 women) used statins (with or without other lipid-lowering drugs). The remaining 8 patients (3 men, 5 women) received no statins. Three of the 113 who died received LDL apheresis in addition to statins.

During lipid-lowering treatment, mean total cholesterol was 6.7 mmol/L (SD 1.5) (men 6.4 mmol/L [SD 1.5]; women 7.0 mmol/L [SD 1.6]). Mean high-density lipoprotein cholesterol was 1.4 mmol/L (SD 0.4) (men 1.2 mmol/L [SD 0.4]; women 1.5 mmol/L [SD 0.3]). Mean LDL cholesterol was 4.7 mmol/L

Table 5. Cancer Mortality in the Unit for Cardiac and Cardiovascular Genetics Registry

Attained Age (y)	Observed Deaths	Expected Deaths	SMR	95% CI
Both sexes				
0 to 19	0	0.19		
20 to 39	2	1.36		
40 to 59	10	13.26	0.75	0.41 to 1.40
60 to 69	12	15.45	0.78	0.44 to 1.37
70 to 79	6	12.33	0.49	0.22 to 1.08
>80	5	4.05	1.23	0.51 to 2.96
Total	35	46.65	0.75	0.54 to 1.05
0 to 69	13	30.27	0.43	0.25 to 0.74
Men				
0 to 19	0	0.11		
20 to 39	0	0.57		
40 to 59	5	5.76	0.87	0.36 to 2.09
60 to 69	8	8.11	0.99	0.49 to 1.97
70 to 79	4	6.28	0.64	0.24 to 1.70
>80	4	1.45	2.76	1.03 to 7.35
Total	21	22.28	0.94	0.61 to 1.45
0 to 69	13	14.55	0.89	0.52 to 1.54
Women				
0 to 19	0	0.09		
20 to 39	2	0.79	2.52	0.63 to 10.07
40 to 59	5	7.50	0.67	0.28 to 1.60
60 to 69	4	7.34	0.55	0.20 to 1.45
70 to 79	2	6.05	0.33	0.08 to 1.32
>80	1	2.60	0.38	0.05 to 2.73
Total	14	24.37	0.57	0.34 to 0.97
0 to 69	11	15.72	0.70	0.39 to 1.26

SMR indicates standardized mortality ratios.

Table 6. Death by Other Causes in the Unit for Cardiac and Cardiovascular Genetics Registry

Attained Age (y)	Observed Deaths	Expected Deaths	SMR	95% CI
Both sexes				
0 to 19	2	1.40	1.42	0.36 to 5.70
20 to 39	4	7.02	0.57	0.21 to 1.52
40 to 59	8	13.36	0.60	0.30 to 1.20
60 to 69	3	9.55	0.31*	0.10 to 0.97
70 to 79	3	10.78	0.28	—
>80	6	7.92	0.76	0.34 to 1.69
Total	26	50.04	0.52*	0.35 to 0.76
0 to 69	28	31.34	0.89	0.62 to 1.29
Men				
0 to 19	2	0.98	2.03	0.51 to 8.14
20 to 39	3	5.10	0.59	0.19 to 1.82
40 to 59	3	8.74	0.34	0.11 to 1.06
60 to 69	2	5.69	0.35	0.09 to 1.41
70 to 79	0	5.24	—	—
>80	2	2.03	0.98	0.25 to 3.93
Total	12	27.80	0.43*	0.25 to 0.76
0 to 69	10	20.52	0.49	0.26 to 0.91
Women				
0 to 19	0	0.42	0.00	—
20 to 49	1	1.91	0.52	0.07 to 3.71
40 to 59	5	4.63	1.08	0.45 to 2.60
60 to 69	1	3.86	0.26	0.04 to 1.84
70 to 79	3	5.53	0.54	0.17 to 1.68
>80	4	5.89	0.68	0.25 to 1.81
Total	14	22.24	0.63	0.37 to 1.06
0 to 69	7	10.82	0.65	0.31 to 1.36

SMR indicates standardized mortality ratios.
*$P<0.05$.

(SD 1.5) (men 4.4 mmol/L [SD 1.4]; women 5.0 mmol/L [SD 1.6]). Mean triglycerides were 1.5 mmol/L (SD 0.6) (men 1.6 mmol/L [SD 0.7]; women 1.4 mmol/L [SD 0.5]). As for clinical signs of hyperlipidemia, data from hospital records were available for 88 of the 113 patients who died. Fourteen patients had verified xanthelasmas and 37 patients had verified xanthomas, whereas the remaining 74 and 51 patients, respectively, did not. There were no significant differences concerning presence of clinical signs and mean death age.

Detailed data on preexisting diseases and mean lipid values were available for 56 of the 113 patients who died. Of these 56 patients, 45 (32 men, 13 women) had preexisting CVD before death, of which 23 (17 men, 6 women) had former myocardial infarction. Seven patients had diabetes mellitus (6 men, 1 woman), and 17 (11 men, 6 women) had hypertension (blood pressure >140/90 mm Hg).

At the time of inclusion in the UCCG Registry, mean total cholesterol was 11.3 mmol/L (SD 2.5) (men 11.4 mmol/L [SD 2.4]; women 11.2 mmol/L [SD 2.5]). Mean high-density lipoprotein cholesterol was 1.3 mmol/L (SD 0.4) (men 1.1 mmol/L [SD 0.3]; women 1.4 mmol/L [SD 0.5]). Mean LDL cholesterol was 9.0 mmol/L (SD 2.6) (men 9.2 mmol/L [SD 2.7]; women 8.8 mmol/L [SD 2.6]). Mean triglycerides were 2.2 mmol/L (SD 2.7) (men 2.9 mmol/L [SD 3.7]; women 1.5 mmol/L [SD 0.7]).

Discussion

No significant differences were noted in all-cause mortality between the FH patients and the general Norwegian population except for a significantly lower SMR in the age group 70 to 79 years. It may be speculated that a selected group of survivors live very healthily. Most FH patients are well aware of premature CVD in the nearest family members and have repeatedly received professional diet and lifestyle advice.

The main difference was in CVD mortality, for which FH patients of both sexes had significantly higher SMRs compared with the general Norwegian population in the age group 0 to 69 years.

In the present study, no FH patients younger than 20 years died of CVD. Epidemiological data has indicated that the first CVD deaths among FH patients appear in the third or fourth decades of life.[8] Because the mean age at inclusion in the UCCG Registry was 54.8 years, the majority of the youngest age group was not included in this registry; therefore, some of the CVD deaths in the younger patients could not be registered in the present study. If all FH patients were diagnosed and included in the UCCG Registry at birth, a higher CVD SMR would be expected.

CVD mortality among FH patients was responsible for 46% of all deaths, whereas in the Norwegian population, CVD was responsible for 37% of deaths in 2010.[19] Mean age of CVD deaths among the FH patients in the UCCG Registry was 62.2 years for both sexes combined, with 57.2 years for men and 67.2 years for women. According to data from the Norwegian Cause of Death Registry, the mean age of CVD deaths in the general population was much higher: 79.0 years from 1992 to 1995 and 81.0 years from 1996 to 2010. In the same time periods, the mean age of CVD deaths was 76.0 years and 78.0 years, respectively, for men and 82.0 years and 85.0 years, respectively, for women. Although it may seem that the mean age of CVD deaths is ≈15 to 21 years younger for FH patients compared with the Norwegian population, these 2 populations are not totally comparable. The FH patient population is slightly younger (mean age 33.6 years at inclusion in the UCCG Registry) than the general Norwegian population (mean age 38.4 in 2001; Statistics Norway). Given equal mortality rates, a lower mean age at death would be expected in a younger population.

Most epidemiological data suggest that long-term lipid-lowering treatment with statins is not associated with the development of cancer, although data on many years of exposure are incomplete.[20–23] Many of the patients in the present study had used statins for >20 years. Thirty percent of them died from cancer, whereas in Norway, cancer was responsible for 35% of all deaths in 2010,[19] suggesting that long-term use of statins does not increase the risk of death from cancer (Table 5).

For death from other causes, FH patients had a significantly lower SMR compared with the Norwegian population. The explanation for this finding is not known. It may be speculated that the FH diagnosis motivates patients to have a healthy lifestyle and regular health checks; however, we cannot rule out unknown confounding factors.

In the UK cohort study with 3382 patients with heterozygote FH, there were 370 deaths from 1980 to 2006.[3] SMRs were calculated before and after January 1, 1992, by which date statins were available for prescription. From 1992 to 2006, coronary mortality was still significantly higher in patients aged 20 to 79 years on statins compared with the general population in England and Wales (SMR 2.13, 95% CI 1.81 to 2.50). There were no significant differences in stroke, but significantly lower mortality in noncoronary heart disease (SMR 0.62, 95% CI 0.53 to 0.72) was noted. Cancer mortality was significantly lower (SMR 0.63, 95% CI 0.50 to 0.79), and there were no significant differences in all-cause mortality.[3] The results are not totally comparable because clinical criteria for FH were used and not strict molecular genetic tests, hence some patients may have been misclassified. Furthermore, the UK study presented specific types of CVD diagnosis, we included all CVD diagnosis in the mortality analysis.

FH is both underdiagnosed and undertreated in the general population.[7] After the Netherlands, Norway has the highest percentage of genetically diagnosed FH worldwide, given an estimated prevalence of 1 in 500[7]; however, only 26% of persons with FH are genetically diagnosed in Norway, based on an estimated prevalence of 1 in 300 with heterozygote FH.[7] Because so many with FH are undiagnosed, the true mortality rates might be different, and even higher SMRs for CVD mortality could be expected.

According to the European Society of Cardiology guidelines for the management of dyslipidemias, treatment is aimed at reaching LDL cholesterol levels <3.5 mmol/L for children and 2.5 mmol/L for adults or, in the presence of CVD or diabetes, <1.8 mmol/L.[7,24] In our study, mean LDL cholesterol after treatment was 4.7 mmol/L, far above the recommended treatment values for FH patients.[24]

According to the World Health Organization, among patients with chronic illnesses, ≈50% do not take medications as prescribed, for various reasons.[25] In our study, at least 12% of those who died did not take statins, and some of them did not receive statins because of end-stage cancer. Many started on lipid-lowering treatment at an advanced age. Patients diagnosed late in life had been exposed to high LDL cholesterol levels for many years, with an increased risk of atherosclerosis. Importantly, the mean age at inclusion in the UCCG Registry was 54.8 years for those who died compared with 33.6 years for the UCCG Registry in total. Mean follow-up time in the UCCG Registry was 6.3 years among the 113

observed deaths compared with 8.0 years for the UCCG Registry in total. This finding suggests that those who died were diagnosed with FH relatively late in life.

In the UCCG Registry, 20.4% of the patients younger than 18 years of age were on lipid-lowering drugs, whereas 89.1% of those aged 18 years and older were on lipid-lowering drugs in the period 1998–2008.[26] The average levels of total cholesterol were 5.7 mmol/L, whereas the average levels of LDL cholesterol were 3.9 mmol/L, and 29.0% of those on lipid-lowering drugs had levels of LDL cholesterol <3.0 mmol/L. The mean age for starting lipid-lowering therapy was 33.4 years.[26]

In Denmark, with a population similar to Norway's, the Copenhagen General Population Study revealed that 48% of FH patients received statins.[27] The risk of CVD was increased 13-fold among untreated FH patients and 10-fold among FH patients on statins.[27] Inadequate and late start of lipid-lowering treatment implied already existing severe atherosclerosis[27] and a higher risk of CVD death.

There were no differences in mutation types in the present study, and the observed deaths had the same 4 mutation types most frequently found among Norwegian FH patients,[4] suggesting that type of mutation was not important for risk of CVD death.

Strengths and Limitations

All Norwegians have a unique identification number that allows for coupling of data across nationwide health registries. Important strengths of this study were the high numbers of FH patients and the complete follow-up. Furthermore, we believe that the FH patients enrolled in the UCCG Registry are representative of the entire Norwegian FH population. About 15 000 persons are expected to have FH in Norway; about one third of the expected FH population were in the UCCG Registry. Data in the UCCG Registry show normal distributions of age and sex. Because the mean age at inclusion was 33.6 years in the UCCG Registry, some severely affected FH patients may have died young before being diagnosed, hence even higher CVD mortality would be expected.

Some of the confounding factors that could influence CVD mortality were not excluded, for example, smoking habits, body mass index, and dietary habits.[28] Our study was limited mainly to a white population. Consequently, it is important to compare these results with similar studies from different countries and among other ethnicities.

The majority of the blood samples were analyzed by the Department of Medical Biochemistry at Oslo University Hospital. A few of the baseline lipid blood samples were taken by the referral doctors and analyzed at local laboratories. Analyses of blood samples from different laboratories may, to a lesser extent, have influenced the results. The latest treatment lipid values were chosen, and mean values were calculated; however, the absence of detailed data on lipids in this study limits the ability to evaluate factors associated with living longer with FH.

This study did not take into consideration change of identification number or emigration to other countries. These factors would not have changed the main findings of our study because only 20 of 4688 patients (0.4%) were lost to follow-up.

Some inaccuracies in the ICD-10 codes made it difficult to establish the exact cause of death. In our study, 2 patients had diabetes mellitus listed as the main death cause. Diabetes mellitus is associated with up to 4 times increased risk of CVD, so it is likely that these 2 persons with FH and diabetes mellitus died of CVD, but it is impossible to be certain.

Conclusion

Despite access to modern dietary counseling and prescribed lipid-lowering drugs, FH patients still have significantly increased CVD mortality compared with the general Norwegian population. It is of great importance to perform new studies to clarify the effects of optimal lipid-lowering treatment on CVD mortality in FH patients.

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Disclosures

None.

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