Cardiovascular disease in patients with genotyped familial hypercholesterolemia in Norway during 1994-2009, a registry study

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Abstract

Aims

Familial hypercholesterolemia (FH) increases the risk for cardiovascular disease (CVD). The primary aim of the present study was to describe incidence and prevalence of CVD leading to hospitalization in a complete cohort of genotyped FH patients.

Methods and Results

In this registry study data on 5 538 patients with verified genotyped FH were linked to data on all Norwegian CVD hospitalizations, and hospitalizations due to pre-eclampsia/eclampsia, congenital heart defects and diabetes. During 1994-2009 a total of 1 411 of these patients were hospitalized, and ischemic heart disease was reported in 90% of them. Mean (SD) age at first hospitalization and first re-hospitalization was 45.1 (16.5) and 47.6 (16.3) years, respectively, with no sex differences (p=0.66 and p=0.93, respectively). Hospitalization was more frequent among FH men (26.9%) than FH women (24.1%) (p=0.02). Median (25^{th}-75^{th} percentile) number of hospital admissions was 4 (2-7) per FH patient, with no sex differences (p=0.87). Despite having FH at the time of hospitalization, the FH diagnosis was registered in only 45.7% of the patients at discharge.

Conclusion

Most CVD hospitalizations were due to ischemic heart disease. There were no significant sex differences in age at first hospitalization or re-hospitalization, which is an important and novel finding. FH patients were about 20 years younger at first time hospitalization compared to the general population. The awareness and registration of the FH diagnosis during the hospital stays were disturbingly low.

Keywords

Familial hypercholesterolemia

Cardiovascular diseases

Registries

Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality,[1] accounting for 46% of all deaths in Europe.[1] Despite decreases in CVD mortality rates in most European countries, CVD hospitalizations have increased since the early 2000s, and are among the highest ranked disease categories in hospital discharges.[1, 2]

Hospital discharge data thus reflect the burden of CVD morbidity.[1] CVD is the most common cause of all hospitalizations in Norway, of which coronary heart disease (CHD) dominates.[3] Annually, about 15 000 Norwegian patients suffer from myocardial infarction (MI), of whom 36% are women.[4] Although the incidence rate of acute MI declined from 2001 to 2009 in Norway,[5] an 11% increase in hospitalization rates was observed in persons < 45 years of age.[5]

Familial hypercholesterolemia (FH) is an inherited disorder with increased LDL cholesterol (LDL-C),[6, 7] and high risk of premature CVD, particularly at a young age.[8, 9] Before the age of 40 years, the risk of CVD death is increased by 5-20 folds, but as the FH patients get older their risk gradually approaches that of the general population.[8, 10, 11] A European study has suggested that the prevalence of FH is inversely related to age in CHD patients with a putative prevalence of 1:5 in those with CHD < 50 years of age, [12] much higher than the prevalence in the general population which is estimated to be about 1:200.[13]

Once diagnosed with FH, patients are recommended lipid lowering treatment according to the ESC guidelines.[13] A 76% overall risk reduction in CHD in statin-treated FH patients has been reported, suggesting these patients no longer have a risk of MI significantly different from that of the general population.[14]

To date, important data have been missing for answering questions about how modern cholesterol-lowering treatment affects CVD morbidity and the prognosis for individuals with

FH. This study aim was to investigate incidence and prevalence of CVD leading to hospitalization in the complete cohort of genotyped FH patients in Norway. We specifically studied if specific subtypes of CVD are more prevalent among FH patients in relation to sex.

Methods

Approvals

This study was performed in accordance with the Declaration of Helsinki and approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (case no. 2011/1343) and the Data Protection Official at Oslo University Hospital.

Study design

This was a registry study of all genotyped FH patients in Norway from January 1, 1992 until May 1, 2014. All FH patients living in this time period were observed for hospitalizations in the time period from January 1, 1994 throughout December 31, 2009. Study endpoint was defined as December 31, 2009. The primary outcome was first time hospitalization due to CVD.

The Unit for Cardiac and Cardiovascular Genetics (UCCG) Registry and the Cardiovascular Disease in Norway (CVDNOR)

Study data were derived from the National UCCG Registry and the CVDNOR database.
In Norway, genetic testing for FH has been performed since 1992. All patients with FH mutations are included in the UCCG Registry after written informed consent. All FH patients are heterozygote except 11 patients who are homozygote.[8]

In CVDNOR (www.cvdnor.no) all hospital stays recorded with a cardiovascular discharge diagnosis or pre-eclampsia/eclampsia, congenital heart defects and diabetes (DM) were retrieved retrospectively from the patient administrative systems at all Norwegian somatic hospitals from January 1,1994 throughout 2009.[22] During this period, there were 4.3 million hospitalizations registered of which women accounted for 46.8%.[15] There were in total 1.3 million patients hospitalized (51.3% women) with a CVD related diagnosis or procedure code,[15] of which 1/3 of them had CHD.[15] Mean (SD) age at first time admission with a CVD related diagnosis was 64.9 (20.2) years: 64.0 (19.0) years in men and 66.0 (21.3) years in women.[16] Mean number of hospital admissions was 3.2: 3.5 for men and 3.0 for women, respectively.[16]

An incident AMI was defined as the first AMI event in an individual with no prior hospitalization due to AMI during the previous seven years.[16] A recurrent AMI was defined as a new event occurring >28 days after the first event.[16] If hospitalization for AMI occurred within 28 days of the first event, it was defined as part of the same event.[16] An AMI event with percutaneous coronary intervention (PCI) was defined as hospitalization due to AMI and PCI procedure code given within 28 days from AMI hospitalization date.[16] An AMI event with coronary artery bypass grafting (CABG) was defined as CABG procedure within eight weeks from the AMI event.[16]

The coding system used for all hospitalizations was the International Classification of Diseases (ICD).[16] From 1994 throughout 1995, the 9th revision was used, and from 1996 the 10th. The diagnostic codes were categorized as either main or secondary diagnosis. For all CVD-related diagnostic and treatment procedures the coding systems; the Norwegian classification of medical procedures; 3rd edition, version 1995 (SIF95), the NOMESCO classification of surgical procedures (NCSP) and the Norwegian classification of medical procedures (NCMP) were used. In 2006 the NCSP and the NCMP were merged.[17] The main

discharge diagnosis was defined as the diagnosis requiring the most resources during a hospital stay. In cases where the same patient was admitted to one hospital ward and later transferred to other wards within the same hospital stay, only the main discharge diagnosis from the first hospital ward was reported. If a patient was re-admitted to the hospital within 24 hours after discharge, this new hospitalization was defined as belonging to the first. If re-admission occurred more than 24 hours after discharge from the first, this was defined as a new hospitalization.[16]

Data collection

Data on hospitalizations in the FH cohort were retrieved from January 1, 1994 throughout December 31, 2009. Variables taken from the UCCG Registry were sex, birth year, date and age of inclusion in the registry. This information was linked to CVDNOR data on age at first hospitalization and re-hospitalizations, admissions and discharge dates, department and ward codes as well as transfer dates and whether the admission was acute or elective. Furthermore, data on CVD related procedures performed during hospital stays were extracted. [16, 17] The definition of diagnoses and CVD related procedures are given in Table 1.

Statistical analysis

Descriptive data are presented as means (SDs) for normal distributed continuous variables and frequencies (%) for categorical variables. For skewed data, median (25^{th} and 75^{th} percentile) is reported.

The FH cohort was linked to hospitalization data from January 1, 1994 throughout December 31, 2009. The hospitalizations in the FH cohort were described based on data extracted from CVDNOR according to sex, birth year and year of hospitalizations. Re-admission in the FH cohort was defined as more than one hospital stay.

Age at hospitalization was calculated by subtracting year of birth from year of hospitalization. Time from inclusion in the UCCG Registry was given according to sex and year of birth. Sex

differences in characteristics between groups were tested by independent *t*-test for continuous variables and chi-square test for categorical variables. For skewed distributions, Wilcoxon rank-sum test was used. As repeated hospitalizations of the same individual leads to dependence between observations of hospitalization, we applied repeated measures logistic regression to test sex differences. Odds ratios (ORs) with 95% confidence intervals (95% CIs) are presented. A Wald test was applied to study interaction between age and sex in the analysis of CVD hospitalizations (Table 5). The total numbers of FH patients hospitalized according to attained age intervals were calculated. All p-values < 0.05 was considered statistically significant. The analyses were performed using STATA 13.1, 12-core Parallel Edition, and the Statistical Package of Social Sciences (SPSS Inc, Chicago, IL) version 22.0.

Results

The FH study sample

From January 1, 1992 until May 1, 2014, the UCCG Registry consisted of 5 538 patients with genotyped FH, of which 2 845 (51.4%) were women and 2 693 (48.6%) were men. By dividing the patients in the FH cohort into quintiles, 1/5 were born before 1952, 1/5 were born 1953-1966, 1/5 were born 1967-1976, 1/5 were born 1977-1990, and 1/5 were born 1991-2009.

Mean (SD) age at inclusion in the UCCG Registry, reflecting the age at time of genetic FH diagnosis, was 33.8 **(**19.0**)** years: 32.5 (18.6) years for men and 35.0 (19.4) years for women ($p<0.001$). Median (25^{th} -75^{th} percentile) time to study endpoint from genetically verified FH diagnosis was 5 (1 – 9) years with no sex differences (p= 0.92).

During 1994-2009, 1 411 (25.4%) of all genotyped FH patients in Norway were hospitalized. Hospitalization was more frequent among FH men (26.9%) than FH women (24.1%) (p=0.02). The characteristics of the hospitalized patients are summarized in Table 2. Re-

hospitalization was recorded for 1 130 of the hospitalized patients (80.1%) and was as common among men as women (p=0.71).

There were no sex differences in the proportion of hospital admissions (p=0.87) or in type of hospitalizations (p=0.86 for acute and p=0.78 for elective admissions), of which elective admissions were dominating (Table 2).

Those who had been hospitalized were older at time of genetic diagnosis than those who had not been hospitalized: mean (SD) 47.6 (16.7) years versus 29.2 **(**17.3**)** years (p<0.001), respectively. The patients were genotyped 8.8 (5.5) years prior to hospitalization (men 9.1 (5.7) and women 8.5 (5.3), p=0.04) (Table 2). Mean (SD) age at first hospitalization and re-hospitalization was 45.1 (16.5) and 47.6 (16.3) years, respectively, with no sex differences (p=0.66 and p= 0.93, respectively).

Of all hospitalized FH patients, 45.7% had FH recorded at discharge. The FH diagnosis was recognized more frequent in men (50.3%) than in women (41.0%) (p<0.001) (Table 2).

The reported comorbidities among the hospitalized FH patients at discharge are summarized in Table 3. CHD was most common (46.8%), followed by acute coronary syndrome (ACS) (25.2%) Altogether 89.6% of all hospitalized FH patients had ischemic heart disease (CHD, AMI and ACS), of which more men (p<0.001). Comorbidity due to heart failure (HF), atrial fibrillation/flutter (AF) and aortic aneurysm (AA) was also more prevalent among FH men than FH women (p≤0.04).

The numbers of hospitalizations in the 1 411 FH patients in relation to sex and the different diagnoses and CVD diagnostic procedures are given in Table 4 with results of age adjusted analysis. FH men had higher odds of CVD hospitalizations than FH women (p<0.001), and of hospitalization due to CHD, ACS, AMI, AA, HF, AF and PCI (p<0.001). There were no significant sex differences in hospitalizations with CABG or coronary angiography.

Table 5 displays CVD hospitalizations in relation to attained age intervals (significant interaction between age and sex, $p_{interaction}$ <0.001). Most hospitalizations were in the age group 40-59 years. FH men had higher odds of hospital stays due to CVD in all age groups as compared to FH women (p<0.001). However, the sex differences were smaller in FH patients ≥ 70 years of age.

Discussion

FH patients were first time hospitalized about 20 years earlier compared to the general population (45.1 versus 64.9 years[16]) with no sex differences in mean age at first hospitalization, which are important and novel findings. However, women were significantly older at time of genetic FH diagnosis compared with men, indicating delayed initiation of statin treatment in FH women.

Despite FH being a contributing factor to CVD events, less than half of all the hospitalized patients had FH registered as any diagnosis at discharge. This finding is important, implying either patient's unawareness of reporting FH once admitted with CVD, or physicians' ignorance of FH, not asking the patient.

Re-admission rates are considered a measure of healthcare quality. [18,19] Most FH patients (80%) had one or more hospital re-admissions which are in accordance with a recent study demonstrating that 70% of FH patients had experienced one or more MIs at time of death.[9] The high number of re-admissions underscores the importance of early interventions and follow-ups. Although re-hospitalizations due to CVD are common and accounting for 29.3% of all cases in Europe,[19] it seems more frequent in the FH population.

Whereas most hospitalizations in Norway are acute admissions (68.0%),[4] elective hospitalizations dominated (60.6%) among the FH patients. Elective re-admissions are usually due to scheduled coronary angiography, PCI or CABG.[18] However, we found no differences

in these procedures in the hospitalized FH patients compared with the general Norwegian population which could be related to the high numbers of elective hospitalizations.[16] Re-admissions may also vary according to length of index stay, residence, sex, age, comorbidity,[18] or be due to complications like arrhythmias, bleedings, and re-infarctions.[20] Once established CVD in young age, higher re-admission rates are expected,[19] and efforts to reduce re-admissions should be targeted in FH patients at high risk of CVD. [20]

During 1991- 2000, the number of AMI hospital admissions in Norway declined by 18%, but from 2000 an increment by 33% was reported which was mainly due to changes in the diagnostic criteria for AMI with the introduction of cardiac troponins.[21] Moreover, there was an increment of patient transfers between hospitals due to higher number of coronary invasive procedures.[22, 21, 23] The number of patients who underwent PCI and CABG increased during 2001-2009 in all age groups,[24] of which men had highest numbers.[24] In the present study FH men had significantly more hospitalizations with PCI compared to FH women. There was no sex differences in hospitalizations due to CABG and coronary angiography, suggesting that CVD risk differs less in FH patients in relation to sex than found in the general population, but the total number of observations (14) was too low for statistical comparison.[16]

Furthermore, the overall few numbers of diagnostic invasive procedures reflect the time period this study covered. From 2000 and onwards rates of MI declined. [25, 26] During 2003-2012 coronary revascularization declined by 40% with most rapid declines in elective PCI and CABG.[26]

We recently reported that 88% of the deceased FH patients in this cohort used statins but did not reach recommended LDL-C target values.[8] In the present study the hospitalized FH patients were about 18 years older at time of diagnosis compared to those who had not been hospitalized, clearly demonstrating the negative impact of a late diagnosis on CVD morbidity. In a subgroup of 4 688 patients in this cohort those who died were about 20 years older at

time of genetic diagnosis than the survivors (mean 54.8 vs 33.6 years).[8] A meta-regression analysis of 25 trials reported a significant positive relationship between reduction in LDL-C and reduction in CVD risk.[27] Notably, statin adherence is associated with a reduction in CVD related hospitalizations and subsequent health care costs.[28]

Strengths and limitations

Important strengths of this study were the high number of genotyped FH patients and the complete follow-up. Although mean age in the FH cohort was slightly younger than in the Norwegian population in the same time period,[8] the link to CVDNOR gave corresponding data from the Norwegian population from the exact same time period. As all CVD hospitalizations from the entire Norwegian population during 1994-2009 were included, potential selection biases were minimized.

The present study may have underestimated the CVD morbidity in the FH population since many with undiagnosed FH are not accounted for. Some may not have been hospitalized for different reasons such as out-of-hospital deaths or less severe forms of CVD misdiagnosed as other disorders.

CVDNOR did not provide information on pharmaceuticals, or data on physician follow-ups. Nor were there available data on AMI subtypes. Important factors that could influence CVD morbidity and hospitalization frequencies were not accounted for, i.e. smoking habits, body mass index, LDL-C values, statin treatment, dietary habits or participation in CVD rehabilitation programs after discharge. However, in a study of 956 patients in this cohort 89.1% of those aged 18 and above used lipid-lowering drugs and the mean levels of total serum cholesterol and LDL-C were 5.7 (1.5) mmol/L and 3.9 (1.3) mmol/L, respectively.[29] Further, our study was mainly limited to a Caucasian population where 92.4% of the patients in the FH cohort were native Norwegians.[15]

In conclusion, Norwegian FH patients are first time hospitalized about 20 years earlier as compared to the general population, with no sex differences in mean age at first hospitalization which are important novel findings. Ischemic heart disease was present in about 90% of all hospitalized FH patients. Once admitted with CVD, FH was registered in less than half of the hospital records at discharge, which suggests a huge unawareness of FH in Norwegian hospitals.

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Conflict of Interest

None of which are related to the contents of this manuscript.

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Table 1. Definition of diagnoses and procedures during 1994-2009

Diagnosis	ICD-9 codes	ICD-10 codes
Familial hypercholesterolemia	272.0	E78.0
Diseases of the circulatory system (cardiovascular disease)	390-459	I00-I99
Coronary heart disease	410-414	I20-I25
Acute coronary syndrome	410, 411	I20.0, I21, I22
Acute myocardial infarction	410	I21, I22
Cerebrovascular disease	430-438	I60-I69
Total stroke	430-434,436	I60-I61, I63-I64(-I63.6)
Aortic aneurysm	441	I71
Hypertension	401-405	I10-I15

Aortic stenosis	424.1	I35.0, I35.2
Atrial fibrillation/flutter	427.3	I48
Heart failure	428	I50.0
Diabetes mellitus	250	E10-E14
Pre-eclampsia and eclampsia	642-642.7	O11, O14, O15
Congenital heart defects	745-747	Q20-Q28
Main diagnostic and treatment procedures	**SIF95***	**NCMP and NCSP†**
Percutaneous coronary intervention	3294, 3236, 3239	FNG, FNG02, FNG05, FNOB00
Coronary angiography/left or right-sided catheterization	3291, 3235, 3228, 3290	FYDB, TFC10, XF911, XF912, XF914, TFC00
Coronary artery bypass grafting	3112-3129	FNA-FNF

*Norwegian classification of medical procedures; 3rd edition, 1995.

†The NOMESCO classification of medical (NCMP) and surgical (NCSP) procedures; NCMP and NCSP were merged in 2006

Table 2. Selected characteristics[*] of n=1411 patients with familial hypercholesterolemia (FH) hospitalized during 1994-2009

	Total	Women	Men	P-value
	n=1411	n=687	n=724	
Age at FH diagnosis[†] (years), mean (SD)	47.6 (16.7)	48.1 (17.9)	47.1 (15.6)	0.28[‖]
Time from genetically verified FH diagnosis[‡] (years), mean (SD)	8.8 (5.5)	8.5 (5.3)	9.1 (5.7)	0.04[‖]
Age at first time hospitalization (years), mean (SD)	45.1 (16.5)	45.3 (17.8)	44.9 (15.2)	0.66[‖]
Age at first re-hospitalizations (years), mean (SD)	47.6 (16.3)	47.7 (17.9)	47.6 (14.7)	0.93[‖]
Patients with re-hospitalizations, n (%)	1130 (80.1)	553 (80.5)	577 (79.7)	0.71[#]
Number of hospital admissions, median (25^{th} and 75^{th} percentile)	4 (2-7)	4 (2-6)	4 (2-7)	0.87[**]
Patients registered with FH as any diagnosis[§] at discharge, n (%)	645 (45.7)	281 (41.0)	364 (50.3)	<0.001[#]

Type of hospitalization:				
Acute admissions, no.	4653	2213	2440	
OR (95% CI)		1.00 (ref)	0.98 (0.78-1.21)	0.86***
Elective admissions, no.	7177	3298	3879	
OR (95% CI)		1.00 (ref)	1.03 (0.84 - 1.27)	0.78***

* Values are given as mean (SD), median (25th and 75th percentile), frequency (%), or odds ratio (OR) with 95% confidence interval (CI), as appropriate.

† Age at FH diagnosis is equal to age at inclusion in the Unit for Cardiac and Cardiovascular Genetics (UCCG) Registry

‡ From inclusion in the UCCG Registry to study endpoint Dec 31, 2009

§ ICD-9: 272.0 or ICD-10:E78.0

|| T-test, p-value men versus women

Chi-square test, p-value men versus women

** Wilcoxon rank-sum test, p-value men versus women

*** Repeated measures logistic regression, p-value men versus women

Table 3. Selected comorbidities* reported in hospitalized patients with familial hypercholesterolemia during 1994-2009

	Total	Women	Men	P-value†
	n=1411	n=687	n=724	
Coronary heart disease	660 (46.8)	248 (36.1)	412 (56.9)	<0.001
Acute myocardial infarction	248 (17.6)	74 (10.8)	174 (24.0)	<0.001
Acute coronary syndrome	355 (25.2)	113 (16.5)	242 (33.4)	<0.001
Aortic stenosis	89 (6.3)	48 (7.0)	41 (5.7)	0.33
Heart failure	98 (7.0)	38 (5.5)	60 (8.3)	0.04
Atrial fibrillation/flutter	138 (9.8)	47 (6.8)	91 (12.6)	<0.001
Diabetes mellitus	101 (7.2)	43 (6.3)	58 (8.0)	0.19
Hypertension	292 (20.7)	148 (21.5)	144 (19.9)	0.49

Cerebrovascular disease	108 (7.7)	55 (8.0)	53 (7.3)	0.66
Total and ischemic stroke	72 (5.1)	38 (5.5)	34 (4.7)	0.50
Aortic aneurysm	36 (2.6)	6 (0.9)	30 (4.1)	<0.001
Pre-eclampsia and eclampsia	67 (4.8)	67 (9.8)	0	
Congenital heart defects	15 (1.1)	8 (1.2)	7 (1.0)	0.73

* Comorbidity reported in hospital records at discharge. Values are given as frequencies(%)

†Chi-square test, p-value men versus women

Table 4. Hospitalizations* in the 1411 patients with familial hypercholesterolemia registered in CVDNOR during 1994-2009

	Total (n=1411)	Women (n=687)		Men (n=724)		P-value[§]
	No./n[†]	No./n[†]	OR (95% CI)[‡]	No./n[†]	OR (95% CI)[‡]	
Cardiovascular disease	4950/1018	1909/435	1.00 (ref)	3041/583	1.92 (1.77-2.07)	<0.001
Coronary heart disease	2653/660	850/248	1.00 (ref)	1803/412	2.52 (2.07-3.07)	<0.001
Acute coronary syndrome	911/355	267/113	1.00 (ref)	644/242	2.61 (2.08-3.29)	<0.001
Acute myocardial infarction	575/248	170/74	1.00 (ref)	405/174	2.69 (2.06-3.52)	<0.001
Cerebrovascular disease	286/108	151/55	1.00 (ref)	135/53	0.91 (0.66-1.25)	0.56
Total stroke	147/72	78/38	1.00 (ref)	69/ 34	0.78 (0.53-1.16)	0.23

Aortic aneurysm	132/36	10/6	1.00 (ref)	122/30	10.60 (4.92-22.83)	<0.001
Hypertension	850/292	449/148	1.00 (ref)	401/144	1.01 (0.81-1.24)	0.95
Aortic stenosis	282/89	160/48	1.00 (ref)	122/41	0.88 (0.65-1.21)	0.43
Heart failure	323/98	120/38	1.00 (ref)	203/60	1.82 (1.31-2.52)	<0.001
Atrial fibrillation/flutter	427/138	124/47	1.00 (ref)	303/91	2.75 (2.06-3.66)	<0.001
Diabetes mellitus	423/101	212/43	1.00 (ref)	211/58	1.20 (0.89-1.61)	0.23
Pre-eclampsia and eclampsia	91/67	91/67	-	0	-	-
Congenital heart defects	34/15	24/8	1.00 (ref)	10/7	0.41 (0.18-0.92)	0.03

Hospitalizations with percutaneous coronary intervention	646/431	187/131	1.00 (ref)	459/300	2.75 (2.15-3.52)	<0.001
Hospitalizations with coronary artery bypass grafting	14/14	4/4	1.00 (ref)	10/10	2.33 (0.72-7.53)	0.16
Hospitalization with Coronary angiography[||]	14/14	7/7	1.00 (ref)	7/7	0.92 (0.32-2.64)	0.87

[*] Hospitalizations less than 24 hours apart are merged before counting. All counts are hospitalizations with the given disease/procedure as main or secondary diagnosis, readmissions included.

[†] No. =number of hospitalizations, n=number of patients.

[‡]Odds ratio (OR) with 95% confidence interval (CI)

[§] Repeated measures logistic regression adjusted for age at hospitalization, p-value men versus women

[||] Left and right-sided catheterization included

Table 5. Cardiovascular disease hospitalizations[*] in 1018[†] patients with familial hypercholesterolemia according to age intervals during 1994-2009

Attained age (years)	Total	Women		Men	
	No./n[‡]	No./n[‡]	OR (95% CI)[§]	No. /n[‡]	OR (95% CI)[§]
0-39	754/187	215/69	1.00 (ref)	539/118	2.43 (1.93-3.05)
40-59	2114/589	733/217	1.00 (ref)	1381/372	2.47 (1.99-3.06)
60-69	1042/295	396 /126	1.00 (ref)	646/169	2.80 (2.22-3.53)
≥70	711/171	441 /101	1.00 (ref)	270/70	1.65 (1.27-2.16)

[*] ICD-9 codes 390-459 and ICD-10 codes I00-I99. All hospitalizations including re-hospitalizations.

[†] 1018 were hospitalized due to cardiovascular disease. Note that numbers do note sum to 1018 due to hospitalizations in more than one age period for some patients.

[‡] No. =number of hospitalizations, n=number of patients.

[§] Odds Ratio (OR), 95% confidence interval (CI)