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Increased risk of heart failure and atrial fibrillation in heterozygous familial hypercholesterolemia

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ABSTRACT

Background and aims: Heart failure (HF) and atrial fibrillation/flutter (AF) are important causes of morbidity and mortality. Subjects with familial hypercholesterolemia (FH) carry a high risk of coronary artery disease (CAD) but it is not known if the risk of HF and AF is increased in FH. The present study investigated the incidence of hospitalization for HF and AF in a genetically verified FH cohort, age 25 years and older, compared to the general population.
Methods: Incidence rates of hospitalization for HF and AF were estimated from national registry data. Standardized incidence ratios (SIRs) were calculated.
Results: 4273 genotyped FH patients (51.7% women) with a total observation period of 18,300 patient years were studied. Overall, the expected number of FH patients with HF was 27.7 and the observed number of cases was 54 (SIR (95% CI) 2.0 (1.5–2.6)). The highest excess risk was observed in the age group 25–49 years, where SIRs were 3.8 (1.2–11.8) and 4.2 (2.0–8.8) in women and men, respectively. The total expected number of FH patients with AF was 39.4 while the observed number of cases was 77 (SIR 2.0 (1.6–2.4)). Among FH patients with an incident event of HF, nearly 90% had a previous diagnosis of CAD, and nearly 40% had suffered from a myocardial infarction.
Conclusions: We demonstrate a doubling of the risk of hospitalization for HF or AF in patients with FH. This is could have an important prognostic impact for patients and economic impact for the society.

1. Introduction

Heart failure (HF) is an important cause of morbidity and mortality globally, and the prevalence is increasing [1,2]. Furthermore, the prevalence of atrial fibrillation/flutter (AF), the most common form of arrhythmia, is also increasing. Indeed, the burden of AF increases in HF and *vice versa*; AF complicates the course of HF [3].

The relationship between low-density lipoprotein (LDL)-cholesterol and cardiovascular disease (CVD) is firmly established [4], and there is an increased risk of coronary artery disease (CAD) in familial hypercholesterolemia (FH) due to increased LDL-cholesterol load [5]. Recently, a risk stratification tool for the risk of CVD in FH patients has been validated [6]. FH patients present earlier with CVD than the general population [7] and CVD mortality is increased in FH [8,9].

CAD is the most common cause of HF in the western world [2],

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thus an increased prevalence of HF in FH patients should be expected. Even so, data regarding HF and AF in FH patients are scarce.

In the present study, the primary aim was to investigate risk of hospitalizations due to HF and AF in a genetically verified FH cohort in comparison with the risk in the entire Norwegian population.

2. Materials and methods

2.1. 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.

2.2. Study design

The study is a prospective cohort study based on linkage between data from the Unit for Cardiac and Cardiovascular Genetics (UCCG) Registry, the Norwegian Cause of Death Registry (NCoDR) and the Cardiovascular Disease in Norway (CVDNOR) project database [10,11]. The three data sources were linked by means of the 11-digit personal identification number, unique to each Norwegian resident.

2.3. The UCCG registry

The UCCG Registry, after written informed consent, captures all genetically confirmed FH cases in Norway since 1992. On December 31st, 2009 there were 8 homozygous, 3 of them with CHD [12]. The FH registry is described elsewhere [5,6,8,11–14]. A total of 4273 patients were included in the registry during 1992–2009.

2.4. Cardiovascular outcomes and study samples

Information on AF and HF among FH patients and in the total Norwegian population were obtained from CVDNOR. The main and supplementary diagnoses were coded according to the International Classification of Diseases (ICD), version 9 until 1998 and version 10 from 1999 and onwards. Since 1951 the NCoDR contains information on date and cause of death (underlying, contributing and immediate causes) for all deaths among Norwegian residents [15]. Causes of death were coded according to ICD-9 until 1995 and ICD-10 from 1996 and onwards.

The study sample was defined separately for analyses of AF and HF. For AF, the study sample was defined as all FH patients registered in the UCCG Registry before December 31st, 2009 and without any known prior AF-hospitalizations. In order to make sure that patients did not have AF at baseline, we used the period 1994–2000 as a wash-out-period to search for previous events, and restricted the analyses of incidence rates and SIR to the period 2001–2009, excluding FH patients with the first occurrence of AF before 2001. A total of 3161 FH patients were included in analyses of AF.

Definition of the study sample for HF was done using corresponding rules of exclusion, with HF instead of AF, leaving 3145 FH-patients for analysis. AF was defined as ICD-9 code 427.3 and ICD-10 code I48. For HF, the definition was ICD-9 code 428 and ICD-10 code I50.

An incident event of AF was defined as a hospitalization with AF as main or secondary diagnosis or a death with AF as the underlying cause of death, without any prior hospitalizations with AF. Patients were followed from inclusion in the FH registry until first occurrence of AF, death or 31st December 2009, whichever came first. The definition of an incident event of HF and calculation of follow-up time for HF were done in the same manner as for AF. The follow-up time for each individual was split over calendar years and the attained age for each individual was updated for each calendar year.

2.5. Statistical analysis

Unadjusted incidence rates were calculated for each endpoint for the time period 2001–2009 stratified by sex and the age groups 25–49, 50–69 and 70+. For each age stratum, the incidence rates were calculated as the number of events per 1000 person/years of follow-up for FH patients and the entire population. Incidence rates for the total Norwegian population during 2001–2009 in one-year sex- and age strata were obtained from CVDNOR. SIRs were calculated for each endpoint with the incidence rates for the total Norwegian population as reference rates [16]. We calculated the expected number of incident events for men and women for each combination of 1-year age group (x) and calendar year (y) in the UCCG Registry as time spent in the cohort multiplied by the incidence rate for the same combination of birth year and calendar year, in the total Norwegian population. The total expected number of incident events for men and women was obtained by indirect standardization, by summing the expected number of deaths over 1-year age groups and calendar years [17].

$$E_p = \sum_{y=2001}^{2009} \sum_{x=25}^{93} T_p(x,y) \cdot R(x,y)$$

T_p denotes time spent in the patient cohort for a specific combination of age (x) and calendar year (y). R denotes the corresponding incidence rate in the total Norwegian population for the same combination of age and calendar year. SIR was calculated as the observed number of events divided by the expected number of events and upper and lower confidence limits were obtained using the normal approximation to the Poisson distribution. SIRs were calculated separately for men and women using the same age-groups as for incidence rates with indirect age-standardization within each age group. For the identified incident cases of AF and HF we searched through CVDNOR-data prior to the incident event to look for previous CVD hospitalizations. All analyses were performed using Stata version 14.

3. Results

From 2001 through 2009 the UCCG Registry included 4273 genotyped patients (51.7% women), with a total observation period of 18,300 patient/years. Mean (SD) age at the time of genetic diagnosis, as a proxy for the age at the latest probable onset of treatment for FH, was 32.7 (18.6) years. Men were diagnosed earlier in life than women, 31.2 (18.1) years for men *versus* 34.1 (18.9) years for women ($p < 0.001$). Many of the participants were previously described with regards to other characteristics [13,15].

The total expected number of FH patients with HF was 27.7 and the observed number of cases was 54 (SIR (95% CI) 2.0 (1.5–2.6)). For young women (25–49 years), the expected number of cases was 0.8 while the observed number was 3.0; corresponding numbers in young men was 1.7 and 7.0 (Table 1). SIRs for HF for different sex and age groups are shown in Fig. 1; of note is the strikingly higher proportion of HF in young compared to older FH patients.

The total expected number of FH patients with AF was 39.4 while the observed number of cases was 77 (SIR 2.0 (1.6–2.4)), and the numbers for the different age groups are shown in Table 2. The corresponding SIRs are shown in Fig. 2, indicating a doubling of risk for the group as a whole.