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High burden of recurrent cardiovascular events in heterozygous familial hypercholesterolemia: The French Familial Hypercholesterolemia Registry

Sophie Béliard[a,b,*], Franck Boccara[c], Bertrand Cariou[d], Alain Carrié[e], Xavier Collet[f], Michel Farnier[g], Jean Ferrières[h], Michael Krempf[d], Noël Peretti[i], Jean-Pierre Rabès[j], Mathilde Varret[k], Alexandre Vimont[l], Sybil Charrière[m], Eric Bruckert[n], French FH Registry group[1]

[a] Aix Marseille Univ, INSERM, INRA, C2VN, Marseille, France
[b] APHM, Department of Nutrition, Metabolic Diseases, Endocrinology, La Conception Hospital, Marseille, France
[c] AP-HP, Hôpitaux de l'Est Parisien, Hôpital Saint-Antoine, Service de Cardiologie Faculty of Medicine, Sorbonne Université, National Institute of Health and Medical Research, INSERM, UMR_S 938, UPMC, Paris, France
[d] L'institut du thorax, Endocrinology Department, CIC 1413 INSERM, CHU de Nantes, Nantes, France
[e] Sorbonne University, Inserm, Institute of Cardiometabolism and Nutrition (ICAN), UMR_S1166, APHP, Department of Biochemistry, Obesity and Dyslipidemia Genetics Unit, Hôpital de la Pitié, Paris, France
[f] INSERM, UMR1048, Institute of Metabolic and Cardiovascular Diseases, University of Toulouse, Toulouse, France
[g] Point Medical and Department of Cardiology, CHU Dijon-Bourgogne, 21000, Dijon, France
[h] Department of Cardiology, INSERM UMR 1027, Toulouse University Hospital, Toulouse University School of Medicine, Toulouse, France
[i] Hospices Civils de Lyon, Department of Pediatric Nutrition, Bron, France
[j] Department of Biochemistry and Molecular Biology, Ambroise Paré Hospital, HUPIFO (APHP/UVSQ-UFR Sciences de la Santé Simone Veil), Boulogne-Billancourt, France
[k] LVTS, INSERM U1148, Paris Diderot University, Paris, 7, France
[l] PHExpertise, Paris, France
[m] Hospices Civils de Lyon, Endocrinology Department, Bron, Lyon1 University, France
[n] Department of Endocrinology and Cardiovascular Disease Prevention, Institute of Cardio Metabolism and Nutrition (ICAN), La Pitié-Salpêtrière Hospital, AP-HP, Paris, France

HIGHLIGHTS

- One in two HeFH patients is not treated with statins at the time of the first CV even.
- 37% of HeFH patients have CV recurrences after a first CV event.
- Nearly half of the CV recurrences occurred more than 3 years after the first event.

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ABSTRACT

Background and aims: Cardiovascular risk is high in heterozygous familial hypercholesterolemia (HeFH). The objective of this study was to describe recurrent cardiovascular events in selected patients with HeFH attending lipid clinics in France.

Methods: We included 781 patients with a clinical (Dutch Lipid Clinic Network score ≥ 6) or genetic diagnosis of HeFH who had experienced a first cardiovascular event (myocardial infarction, percutaneous coronary intervention or coronary bypass, unstable angina, stroke, peripheral arterial revascularization or cardiovascular death) and were enrolled in the French Familial Hypercholesterolemia Registry (November 2015 to March 2018).

Results: The first cardiovascular event occurred at the mean age of 47 years (interquartile range 39–55) in a predominantly male population (72%); 48% of patients were on statin therapy. Overall, 37% of patients had at least one recurrent cardiovascular event (mean of 1.8 events per patient), of which 32% occurred in the 12 months after the index event; 55% of events occurred > 3 years after the first event. Mean LDL-C at the last clinic

* Corresponding author. APHM, Department of Nutrition, Metabolic diseases, Endocrinology, La Conception Hospital, 147 boulevard Baille, 13005 Marseille, France
E-mail address: sophie.beliard@ap-hm.fr (S. Béliard).

[1] French FH Registry group: D. Angoulvant, S. Béliard, P. Benlian, C. Boileau, F. Boccara, E. Bruckert, B. Cariou, V. Carreau, A. Carrié, S. Charrière, M. Di Filippo, PH. Ducluzeau, S. Dulong, V. Durlach, M. Farnier, E Ferrari, J. Ferrières, A. Gallo, JP. Girardet, R. Hankard, M. Krempf, JD. Lalau, B. Lefort, J. Lemale, P. Moulin, F. Paillard, N. Peretti, A. Pradignac, Y. Pucheu, JP. Rabès, S. Saheb, A Sultan, P. Tounian, R. Valéro, M. Varret, B. Vergès, C Yelnik, O. Ziegler.

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visit was 144 ± 75 mg/dL (132 ± 69 mg/dL for patients on high-potency statin therapy and 223 ± 85 mg/dL for untreated patients).
Conclusions: The rate of recurrent cardiovascular events was high in French patients with HeFH in secondary prevention. The detection of FH during childhood is crucial to prevent CV events at a young age by early initiating statin therapy. There is a clear urgent need to expand the actual very small target population which can be treated with the PCSK9 inhibitor in France.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant hereditary disease caused by mutations in genes involved in the catabolism of low-density lipoprotein cholesterol (LDL-C): *LDLR*, *APOB* and *PCSK9* [1,2]. FH is one of the most common genetic diseases, with an estimated prevalence of 1 in 250 for heterozygous FH (HeFH) and 1 in 300,000 for homozygous FH [3–5]. People with FH have very high circulating levels of LDL-C from birth, leading to a lifelong exposure of the arteries to elevated levels of cholesterol and a high cardiovascular risk [6,7]. Young adults with FH have an up to 13-fold higher risk of myocardial infarction compared to similar young adults without condition [3,4]. As placebo-controlled randomized trials with cardiovascular endpoints are unethical in FH, the reduction in cardiovascular risk with lipid-lowering treatment has to be extrapolated from trials in the general population or from observational studies [8–10].

The current burden of cardiovascular disease in patients with HeFH in France is unknown. We sought to evaluate the typical features of cardiovascular disease (mean age at the time of the event, type and number of events, use of lipid-lowering therapies) in HeFH patients in secondary prevention in the French Familial Hypercholesterolemia Registry.

2. Patients and methods

2.1. Settings

In 2015, the New French Society of Atherosclerosis established a national multicenter registry to identify patients with FH in France, with the objective of assessing screening practices, treatments, and clinical and patient-reported outcomes. Eligible patients were those who visited a participating lipid clinic and were diagnosed, either clinically (Dutch Lipid Clinic Network score ≥6) or genetically, with homozygous or heterozygous FH.

Sixteen sites contributed data to the registry, as of March 2018. Adult patients received an information leaflet about the registry before being evaluated for inclusion. Informed consent from both parents was required in the case of minors. The cohort was declared to the ANSM (the French National Agency for Medicines safety) and received a declarant number [unique number identifying a particular research protocol, issued by the ANSM in France]: 2014-A01549-38. The protocol of this study was assessed by two different committees: French advisory committee on the processing of information for medical research (CCTIRS) and the National Commission for computer technology and freedom (CNIL) respectively in May and November 2015. This research is conducted in accordance with good clinical practices.

Clinical and laboratory data from the patients' medical records were obtained during routine clinic visits and were entered into the registry database by trained research staff. To obtain data from first contact, retrospective data extraction from the patients' medical records was done for patients who were already being treated at the site.

Sociodemographic, clinical and biological data (age, height, weight, blood pressure, smoking status, cardiovascular events, use of lipid-lowering drugs) were collected, along with family history (hypercholesterolemia or any cardiovascular disease), standard laboratory results (total cholesterol, LDL-C) and cardiovascular imaging data. Where available, genetic data (presence of known FH-related mutations) were collected. Information on cardiovascular history included the date of diagnosis and the type of event. Cardiovascular events included coronary heart disease (acute coronary syndromes, encompassing myocardial infarction and unstable angina, defined according to the European Society of Cardiology/American College of Cardiology [11], percutaneous coronary intervention or coronary artery bypass graft), stroke or transient ischemic attack, peripheral artery disease (defined as carotid endarterectomy, carotid angioplasty, peripheral artery angioplasty or bypass), resuscitated sudden death and cardiovascular death.

2.2. Patients and outcomes

The present analysis involved patients with either a Dutch Lipid Clinic Network score ≥6 or an FH-causing mutation, plus a history of at least one cardiovascular event. Cardiovascular event and recurrences of cardiovascular events were defined as: coronary heart disease (myocardial infarction, coronary angioplasty or bypass and unstable angina), stroke, transient ischemic attack, peripheral artery disease (carotid endarterectomy, carotid angioplasty, and peripheral arterial bypass), resuscitated sudden death or cardiovascular death. A recurrent cardiovascular event was defined as a second cardiovascular event, regardless of the type of the first or the second event. Coronary revascularization (i.e. percutaneous coronary intervention or coronary artery bypass graft) and myocardial infarction occurring < 30 days after the index event were not considered as recurrences.

Overall follow-up duration was defined as the time from the first cardiovascular event to the last available visit at the lipid clinic. The length of time between the first and the last available visit was also assessed. Exclusion criteria were a diagnosis of homozygous FH and the occurrence of minor cardiovascular events such as silent ischemia and stable angina when not followed by coronary revascularization.

2.3. Statistical analysis

Data are presented as frequency and percentage for categorical variables and as mean (standard deviation [SD]) or median with interquartile range (IQR) for continuous variables. A descriptive analysis was performed for cardiovascular event history. The characteristics of patients with and without at least one recurrence were compared using Student's *t*-test or the Wilcoxon rank-sum test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. *p* values were associated with a significance level of 0.05 for all tests. All analyses were performed with SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Between November 2015 and March 2018, 4682 patients were enrolled in the registry, of which 781 (16.7%) met the inclusion criteria. The characteristics of the population (at the last clinic visit) are detailed in Table 1. Median follow-up was 7 (IQR: 2-17) years from the time of the first cardiovascular event until the last available clinic visit, totaling 5779 patient-years of follow-up. The population was predominantly male (72%) with a mean age of 60 years, and 64% had a family history of any cardiovascular event. Over half (55%) of the patients had a