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Prevalence and management of familial hypercholesterolemia in patients with coronary artery disease: The heredity survey

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ABSTRACT

Background and aims: Familial hypercholesterolemia (FH) is a genetic disorder characterized by high levels of low density lipoprotein cholesterol (LDL-C) predisposing to premature cardiovascular disease. Its prevalence varies and has been estimated around 1 in 200–500. The Heredity survey evaluated the prevalence of potential FH and the therapeutic approaches among patients with established coronary artery disease (CAD) or peripheral artery disease (PAD) in which it is less well documented.

Methods: Data were collected in patients admitted to programs of rehabilitation and secondary prevention in Italy. Potential FH was estimated using Dutch Lipid Clinic Network (DLCN) criteria. Potential FH was defined as having a total score ≥ 6.

Results: Among the 1438 consecutive patients evaluated, the prevalence of potential FH was 3.7%. The prevalence was inversely related to age, with a putative prevalence of 1:10 in those with <55 yrs of age (male) and <60 yrs (female). Definite FH (DLCN score > 8) had the highest percentages of patients after an ACS (75% vs 52.5% in the whole study population). At discharge, most patients were on high intensity statin therapy, but despite this, potential FH group still had a higher percentage of patients with LDL-C levels not at target and having a distance from the target higher than 50%.

Conclusions: Among patients with established coronary heart disease, the prevalence of potential FH is higher than in the general population; the results suggest that a correct identification of potential FH, especially in younger patients, may help to better manage their high cardiovascular risk.

1. Introduction

Familial hypercholesterolemia (FH) is a genetic-based disease characterized by premature atherosclerotic disease due to the presence of high low density lipoprotein cholesterol (LDL-C) levels from birth [1–3]. Mutations in the gene encoding the receptor for LDL (LDLR) are the most common cause of FH, but mutations in other genes involved

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in LDL metabolism, including proprotein convertase subtilisin/kexin type 9 (PCSK9) and apolipoprotein B, may lead to similar phenotypes [4]. In the general population, the frequency of homozygous FH, requiring therapeutic intervention in the first decade of life, is very low (1:1,000,000) [2,4]. On the contrary, heterozygous FH in Caucasians is more common; historically, its prevalence was estimated at 1 in 500, but more recent studies suggest a higher frequency, up to 1 in 200–250 [5]. Because of the exposure to high levels of LDL-C from birth (200–400 mg/dL; 5–10 mmol/L), FH subjects have a significantly greater risk of cardiovascular disease and, if untreated, they may experience cardiovascular events early in the life [6]. Thus, the identification of FH subjects is critical for the prevention of coronary heart disease through early and effective therapeutic approaches. Despite this, the identification of patients with heterozygous FH is still partial in Europe, in particular in Italy [2].

Different criteria have been proposed to allow the detection of FH patients, including the Simon Broome Register Diagnostic criteria [7], the MedPed/WHO criteria [8] and the Dutch Lipid Clinic Network (DLCN) Diagnostic criteria [9]. These algorithms are mainly based on the blood LDL-C levels, a positive family history of coronary artery disease (CAD), personal CAD history and physical signs [7–9].

Recently, it was shown that among patients with CAD or other atherosclerotic diseases the frequency of FH is significantly higher than in general population and that these patients are at particularly elevated risk of recurrent events [10–12]. In particular, the post hoc analysis of EUROASPIRE IV reported an increased prevalence of potential FH in coronary patients from 24 European countries by means of standardized interview and biochemical and clinical examination using an adapted version of the DLCN criteria [10]. However, this study did not include Italian patients; to overcome this lack, we designed the "HEterozygous familial hypeRcholesterolemia in patiEnts admitted to carDiac rehabilitaTion programs in Italy" (HEREDITY) survey through Italy's national network of cardiac rehabilitation and secondary prevention (CRP) centres. This survey aimed at investigating the prevalence of heterozygous FH using the DLCN criteria among "real world" patients with CAD or peripheral artery disease (PAD) admitted to programs of rehabilitation and secondary prevention. Potential FH patients, defined as having a Dutch score ≥ 6, were compared with the other patients and evaluated at discharge. Moreover, this study evaluated the therapeutic approaches and the results obtained in terms of recommended lipid target values.

2. Methods

2.1. Study design

The HEREDITY survey was an observational multicentre nationwide survey involving 26 in- and out-patients CRP units. Each participating centre was asked to provide clinical and biochemical data of at least 50 consecutive patients discharged (between February and March 2015), in order to ensure the expected sample size (>1000 patients), after a CRP program (4–8 weeks of duration) for recent (within 2 weeks) acute coronary syndrome (ACS) and/or percutaneous/surgical myocardial revascularization or stable angina with medical therapy or for lower extremity PAD with or without recent acute event.

Electronic case report forms (eCRF) were used for data entry, and data were transferred via web to a central database. Patients' anonymity was ensured. The eCRF were collected and data were analysed in relation to the characteristics of patients (sex, age, BMI), admission diagnosis, CRP setting (inpatients or outpatients), co-morbidities, global risk profile, drug therapy and biochemical parameters including total cholesterol, LDL-C, HDL-C, triglycerides (TG) and glycaemia values at discharge. Total cholesterol, HDL-C and TG were measured by local laboratories, all accredited by ISO 15189:2003 (Medical Laboratories - Particular requirement for quality and competence). LDL-C was calculated according to the Friedewald's formula. The prevalence of FH was estimated using the DLCN criteria [2].

Since a large majority of the patients (80.3%) were on statin therapy for at least four weeks at the moment of blood sampling at admission to CRP program, the LDL-C levels obtained were adjusted by correction factors taking into consideration the type and dose of statin [11,13].

The results of the algorithm were interpreted as follows: unlikely FH, total score 0–2; possible FH, total score 3–5; probable FH, total score 6–8; definite FH, total score > 8. Potential FH were defined as having a total score ≥ 6.

Local Ethical committees approved the study. All patients provided written informed consent. The survey involved no diagnostic tests, care interventions or pharmacological treatments that were not part of the routine clinical practice of each participating centre, and each physician enrolling a patient was fully responsible for his/her management. The survey was independently conducted and the data were analysed under the scrutiny of the Steering Committee of the study.

2.2. Statistical methods

We expected to enroll a total sample of approximately 1000 patients. According to the literature data, we hypothesized a prevalence of heterozygous FH of approximately 5% in our study population, thus allowing to obtain a sample of about 50 patients with probable-definite FH. All data collected in the online database underwent data cleaning and quality control. Continuous variables were expressed as mean ± standard deviation (SD) and median (range), categorical variables as number and percentage. Enrolled patients were analysed both as a whole population and by single FH probability class. Patients were also analysed by comparing the group of potential FH having a Dutch score ≥ 6 (probable FH + definite FH) with all the other patients (unlikely FH + possible FH).

Differences between these groups were tested by the Fischer's exact test or Chi Square (categorical data) and by Student's *t*-test (continuous numeric data). All computations were carried out with SAS® statistical software (SAS Institute, Cary, NC, USA – version 9.2) and a $P < 0.05$ was considered significant.

3. Results

This survey included a total of 1438 patients recruited from 26 CRP centres (Appendix). Clinical characteristics of the patients participating in this study are presented in Table 1. Men were 83.7% of the sample; mean age of the whole study population was 65.9 ± 10.6 years, and more than one fourth of total population (429 out of 1438, 29.8%) was ≤60 years old. Recent ACS, with or without percutaneous myocardial revascularization, was the most common clinical presentation (52.5%), followed by stable CAD on medical therapy (26.5%) and symptomatic chronic CAD undergoing surgical or percutaneous myocardial revascularization (18%); isolated lower extremity PAD was the least common presentation (3.1%) (Table 1).

Table 2 reports the prevalence for the different categories of FH according to DLCN criteria by gender, age and entry diagnosis. Considering the whole population, 53 patients (3.7%) had a score ≥ 6 (potential FH) and 12 (0.8%) had a score > 8 (definite FH). Patients with potential FH

Table 1
Characteristics of patients participating in the study.

	Total patients	
N	1438	
Men	1203	83.7%
Women	235	16.3%
Mean age (y ± s.d.) total	65.9 ± 10.6	
Male	65.0 ± 10.3	$P < 0.0001$
Female	70.2 ± 10.9	
Setting		
Outpatients	750	52.2%
Inpatients	688	47.8%
Entry diagnosis		
LE-PAD	46	3.2%
Stable CAD	381	26.5%
Post-ACS	755	52.5%
PCI/CABG without ACS	259	18.0%
Co-morbidities		
No	490	34.1%
Yes	948	65.9%
Risk factors		
None	22	1.5%
Dyslipidemia	1265	88.0%
Family history of CAD	549	38.2%
Hypertension	1010	70.2%
Diabetes	424	29.5%
Smoking	880	62.2%
Sedentary habits	670	46.6%
Obesity	368	25.6%

LE-PAD: lower extremity peripheral arterial disease; CAD: coronary artery disease; PCI/CABG: percutaneous coronary intervention/coronary artery bypass surgery; ACS: acute coronary syndrome.