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Prevalence and management of familial hypercholesterolaemia in coronary patients: An analysis of EUROASPIRE IV, a study of the European Society of Cardiology

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ABSTRACT

Background: Familial hypercholesterolaemia (FH) is a hereditary disorder predisposing to premature coronary heart disease (CHD) and is until now mainly diagnosed clinically on the basis of a classical phenotype. Its prevalence varies and is estimated around 1 in 200–500; in patients with established CHD the prevalence is less well documented.

Methods and results: In EUROASPIRE IV data were collected in coronary patients from 24 European countries by means of a standardized interview, bioclinical examination and venous blood sampling. Potential FH was estimated using an adapted version of the Dutch Lipid Clinic Network Criteria.

Among the 7044 patients eligible for analysis, the prevalence of potential FH was 8.3%; 7.5% in men and 11.1% in women. The prevalence was inversely related to age with a putative prevalence of 1:5 in those with CHD <50 yrs of age in both sexes. Even among women aged 70 the prevalence was 1:10. Irrespective of age and gender, prevalence differed substantially between European regions; potential FH patients were more likely to smoke, had higher triglycerides levels and their blood pressure was less well controlled. The use of cardioprotective drugs and the prevalences of diabetes, obesity and central obesity were similar.

Conclusions: The prevalence of potential FH in coronary patients is high; the results underscore the need to promote identification of FH in CHD patients and to improve their risk factor profile.

1. Introduction

Dyslipidaemias represent a heterogeneous group of disorders that are related to genetic and environmental factors. Familial forms can arise from mutations in one or different genes. Already more than 40 years ago J.L Goldstein et al. [1] had observed that three of these disorders – familial hypercholesterolaemia (FH), familial hypertriglyceridaemia and familial combined hyperlipidaemia – occurred in about 20% of survivors of a myocardial infarction below 60 yrs of age and in 7% of the older survivors. In this report attention is given to the prevalence and management of potential FH in a large group of coronary patients.

FH is an autosomal co-dominant inherited disorder of lipoprotein metabolism characterized by high low density lipoprotein cholesterol (LDL-C) plasma levels from birth and an increased risk of premature coronary heart disease (CHD). Mutations in the gene encoding the LDL receptor (*LDLR*) are the most commonly identified in these patients although mutations in *APOB* and *PCSK9* have also been shown to result in FH. Historically, FH has been diagnosed clinically and the classical phenotype of heterozygous FH was a

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patient with premature CHD, severely elevated LDL-C, a family history of premature CHD and tendon xanthomas. Genomic analysis to identify mutations in the *LDLR, APOB* or *PCSK9* is readily available, but the application of genetic screening varies considerable across countries. Homozygous FH is rare requiring therapeutic interventions in the first decade of life and while the prevalence was believed to be ~1 in 1million current estimates suggest that the figure could be as high as ~1 in 250 000 [2–4].

Heterozygous FH (HeFH) is more common; historically its prevalence was estimated at 1 in 500 people; however, results from more recent studies suggest a higher prevalence up to 1 in 200–250 [5]. The phenotype of HeFH comprises particularly high levels of LDL-C in the range of 5–10 mmol/L (200–400 mg/dL) in adulthood. The identification of patients with HeFH is still very incomplete in Europe and different criteria have been proposed (the Simon Broome Register Diagnostic Criteria [6], the MedPed/WHO Criteria [7] and the Dutch Lipid Clinic Network (DLCN) Diagnostic Criteria [8]) to aid diagnosis. These algorithms are mainly based on the measured LDL-C level, a positive family history of CHD, personal CHD history and physical signs. Patients with established CHD and HeFH are at particularly elevated risk of recurrent events and current management of these patients focuses on the use of potent statins and ezetimibe in order to reach at least a 50% reduction and/or an LDL-C level of <1.8 mmol/L (70 mg/dL). In patients where these targets cannot be reached by statins alone or in case of statin intolerance, other drug treatments or combinations have been suggested in clinical guidelines [9].

Recognizing potential FH patients is of importance for two reasons: firstly, the absolute lifetime cardiovascular risk is sharply increased in HeFH patients and the need for intensive preventive strategies to mitigate this risk are deemed crucial; secondly, by means of cascade screening unidentified affected relatives can be detected. A major challenge therefore in clinical practice is to raise awareness of potential HeFH and identify potential patient groups where HeFH is particularly over-represented which would in turn assist cascade screening.

In order to address some of these uncertainties we aim to estimate the prevalence of clinical HeFH in a large group of patients with CHD who participated in the EUROASPIRE IV survey. Moreover, we compared these potential HeFH patients with the other patients with respect to different clinical characteristics and their management.

2. Study population and methods

2.1. The EUROASPIRE IV survey

The design and methodology of the EUROASPIRE IV study have been described in detail [10] The survey was performed in 24 European countries; patients aged ≥ 18 and <80 years who had been hospitalized for a coronary event (defined as an acute myocardial infarction, acute myocardial ischaemia or procedure [CABG, PCI]) between 6 months and 3 years before the interview, were eligible. They were invited to participate in an interview during which trained technicians collected information through standardized methods.

Height and weight were measured in light indoor clothes without shoes (SECA scales 701 and measuring stick model 220). Obesity was defined as a body mass index ≥30 kg/m^2.

Waist circumference was measured using a metal tape applied horizontally at the point midway in the mid-axillary line between the lowest rim of the rib cage and the tip of the hip bone (superior iliac crest) with the patient standing. Central obesity was defined as a waist circumference ≥88 cm for women and ≥102 cm for men.

Blood pressure was measured twice on the right upper arm in a sitting position using an automatic digital sphygmomanometers (Omron M6) and the mean was used for all analyses.

Breath carbon monoxide was measured in ppm using a smokelyser(Bedfont Scientific, Model Micro +). Smoking at the time of interview was defined as self-reported smoking, and/or a breath carbon monoxide exceeding 10 ppm. Persistent smoking was defined as smoking at interview among patients reporting to be smokers in the month prior to the index event. Habitual physical activity was assessed by means of the International Physical Activity Questionnaire (IPAQ). High physical activity was defined as proposed in http://www.ipaq.ki.se/scoring.pdf.

All patients were asked to come fasting for 10–12 h and the fasting time was recorded at interview. The analyses with LDL-C and triglycerides were limited to those patients fasting for at least 6 h. Venous blood samples were taken with the patients in a sitting position with light stasis into a tube containing clot activator (Venosafe, Terumo Europe, Leuven, Belgium) for lipid assays and into a potassium EDTA tube (Venosafe) for HbA1c assay. Serum was separated by centrifuging at 2000 g for 10 min at room temperature. After that serum was aliquoted into two bar-code-labelled tubes and stored together with whole EDTA blood tubes locally at a minimum of −70 °C and then transported frozen to the central laboratory where all measurements were performed on a clinical chemistry analyzer (Architect c8000; Abbott Laboratories, Abbott Park, Illinois, USA).

Total cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides were analysed in serum, and HbA1c in whole blood with the following methods: enzymatic method for total cholesterol, a homogenous method for direct measurement of HDL-C, an enzymatic glycerol phosphate oxidase method for triglycerides, and an immunoturbidimetric method for HbA1c. LDL-C was calculated according to Friedewald's formula; if the triglycerides level was >4 mmol/L patients were excluded from this analysis.

The central laboratory was the Disease Risk Unit, National Institute for Health and Welfare, Helsinki, Finland, and is accredited by the Finnish Accreditation Service and fulfils the requirements of the standard SFS-EN ISO/IEC 17025:2005.

The laboratory takes part in Lipid Standardization Program organized by CDC, Atlanta, Georgia, USA and External Quality Assessment Schemes organized by Labquality, Helsinki, Finland. During the course of the study, comprising two months in 2013, the coefficient of variation (mean ± SD) and systematic error (bias) (mean ± SD) were 1.3% ± 0.2 and 1.7% ± 1.1 for total cholesterol, 1.6% ± 0.5 and −1.5% ± 1.6 for HDL-C, 2.3% ± 0.1 and −1.2% ± 2.6 for triglycerides, and 1.9% ± 0.1 and 1.4% ± 0.2 for HbA1c, respectively.

2.2. Diagnostic criteria for potential FH

The prevalence of FH was estimated using a modified version of criteria used in the MedPed/WHO algorithm [7] and by the DLCN [8]; 2 points were given if the age at the index event was <55/60 years for men/women OR if self-reported age of first diagnosis of CHD was <55/60 years for men/women; 1 point was given for a positive family history of premature (<55/65 years for men/women) CVD. The presence of arcus cornealis or tendon xanthomata was not recorded in the EUROASPIRE IV survey. A large majority of the patients (85.7%) was on statin therapy at the moment of blood sampling. To estimate the “untreated” LDL-C plasma level in these patients, information on the current intake of statins was collected. Participants were asked to bring all the drugs that they were taking on a daily basis to the interview and the interviewer collected the data regarding the dose; in case the interview was done at the home of the patients, detailed information was also collected as to the type of statin and the dosage. At the interview there was one question on compliance: “In the past month how often did you take your medication?” Possible answers were: “all the time (100%); nearly all of the time (90%); most of the time