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Genetically Confirmed Familial Hypercholesterolemia in Patients With Acute Coronary Syndrome

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ABSTRACT

BACKGROUND Genetic screening programs in unselected individuals with increased levels of low-density lipoprotein cholesterol (LDL-C) have shown modest results in identifying individuals with familial hypercholesterolemia (FH).

OBJECTIVES This study assessed the prevalence of genetically confirmed FH in patients with acute coronary syndrome (ACS) and compared the diagnostic performance of FH clinical criteria versus FH genetic testing.

METHODS Genetic study of 7 genes (*LDLR*, *APOB*, *PCSK9*, *APOE*, *STAP1*, *LDLRAP1*, and *LIPA*) associated with FH and 12 common alleles associated with polygenic hypercholesterolemia was performed in 103 patients with ACS, age ≤65 years, and LDL-C levels ≥160 mg/dl. Dutch Lipid Clinic (DLC) and Simon Broome (SB) FH clinical criteria were also applied.

RESULTS The prevalence of genetically confirmed FH was 8.7% (95% confidence interval [CI]: 4.3% to 16.4%; n = 9); 29% (95% CI: 18.5% to 42.1%; n = 18) of patients without FH variants had a score highly suggestive of polygenic hypercholesterolemia. The prevalence of probable to definite FH according to DLC criteria was 27.2% (95% CI: 19.1% to 37.0%; n = 28), whereas SB criteria identified 27.2% of patients (95% CI: 19.1% to 37.0%; n = 28) with possible to definite FH. DLC and SB algorithms failed to diagnose 4 (44%) and 3 (33%) patients with genetically confirmed FH, respectively. Cascade genetic testing in first-degree relatives identified 6 additional individuals with FH.

CONCLUSIONS The prevalence of genetically confirmed FH in patients with ACS age ≤65 years and with LDL-C levels ≥160 mg/dl is high (approximately 9%). FH clinical algorithms do not accurately classify patients with FH. Genetic testing should be advocated in young patients with ACS and high LDL-C levels to allow prompt identification of patients with FH and relatives at risk. (J Am Coll Cardiol 2017;70:1732–40) © 2017 by the American College of Cardiology Foundation.

Familial hypercholesterolemia (FH) is an autosomal dominant inherited genetic disorder with a prevalence historically estimated to be on the order of 1:500, but recent data suggest that it could be between 1:200 and 1:250 (1-3). Patients with FH have elevated levels of total cholesterol and low-density lipoprotein (LDL) particles, as well as increased low-density lipoprotein cholesterol (LDL-C) arterial deposits, leading to coronary heart disease (CHD) (4,5).

Patients with FH have cardiovascular complications at an early age and a reduced life expectancy (6,7).

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Early diagnosis followed by an aggressive cholesterol-lowering treatment regimen could prevent occurrence of cardiovascular events by reducing the long-term exposure of these patients and their affected relatives to high levels of LDL-C.

Diagnosis of FH was traditionally based on clinical algorithms, and several groups have developed clinical diagnostic criteria for identification of FH. Among the most widely used FH clinical criteria are those of the Simon Broome (SB) Register Group in the United Kingdom (8) and the Dutch Lipid Clinic (DLC) Network (9).

Advances in genetic testing have made FH genetic testing affordable, but recent studies have shown that FH diagnosis with the use of genetic testing in severely hypercholesterolemic individuals from the overall population is low (between 0.3% and 1.7%) (10,11). This low prevalence suggests a need to identify additional high-risk groups of patients for FH genetic testing. As such, patients with an acute coronary syndrome (ACS) may represent an optimal group for whom FH screening programs could be developed.

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Although the prevalence of genetically confirmed FH in patients with ACS has not been studied in detail, recent European data found a prevalence between 1.6% and 8.3% in this group of patients when using clinical algorithms (12–14). Patients with ACS and FH are at particularly elevated risk for recurrent cardiovascular complications (12), and current management of these patients focuses on aggressive lipid-lowering strategies. Prompt identification of FH among patients with ACS could be extremely useful to allow early intensification of lipid-lowering treatment and might lead to early identification of relatives with FH who have not yet experienced cardiovascular events but who would benefit from early initiation of intensive lipid-lowering therapies (9,15,16).

The goal of the present study was to determine the prevalence of genetically confirmed FH in patients with ACS and to evaluate the diagnostic performance of FH clinical criteria compared with FH genetic findings.

METHODS

Clinical records were reviewed for all patients ≤65 years of age hospitalized at Hospital Universitario Puerta de Hierro (Madrid, Spain) for ACS from January 1, 2012, to March 31, 2016. All patients with actual or estimated LDL-C levels ≥160 mg/dl (4.14 mmol/l) on admission were contacted and offered FH genetic testing. In all patients receiving statin therapy or ezetimibe before admission, LDL-C levels were estimated by multiplying their LDL-C level on treatment with correction factors considering the drug and its dose, as previously reported (17–19). The effect of other lipid-lowering drugs was not considered.

Levels of LDL-C were calculated according to the Friedewald formula (20). Patients were excluded from the study if their triglyceride levels were >350 mg/dl (4 mmol/l). Patients without information on cholesterol levels at admission and those with lipid disorders secondary to renal, thyroid, or liver diseases were also excluded.

Whole blood or saliva samples for deoxyribonucleic acid (DNA) analysis were collected from patients who were accepted into the study and, simultaneously, data about their personal and family history were collected, and a physical examination was performed. The patient selection process is represented in the flowchart in **Figure 1**. The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of Hospital Universitario Puerta de Hierro. All participants gave written informed consent to participate in the study.

FH CLINICAL CRITERIA. The clinical diagnosis of FH was based on 2 widely used FH clinical criteria recommended by international guidelines. The SB criteria (8), recommended by the United Kingdom's National Institute for Health and Care Excellence guidelines, considers a diagnosis of possible FH as a total cholesterol level >290 mg/dl or LDL-C level >190 mg/dl, plus a family history of premature coronary artery disease. A definite FH diagnosis requires the aforementioned cholesterol levels and the presence of tendon xanthomas in the patient or relatives (physical signs of hypercholesterolemia). The DLC criteria (9), endorsed by the European Society of Cardiology, the National Lipid Association in the United States, the International FH Foundation, and the European Atherosclerosis Society, considers LDL-C levels, physical signs, and a personal or family history of premature CHD (Online Tables 1 and 2). Possible FH is defined according to a DLC criteria score of 3 to 5 and probable to definite FH by using a score ≥6. Both sets of criteria include genetic findings among the parameters to consider (which would, per se, at least for DLC clinical criteria, generate a definite diagnosis of FH). Because genetic information is usually not available for most clinicians, and because we wanted to compare the diagnostic performance of genetic testing versus clinical criteria, genetic information was not considered when calculating FH clinical criteria by both algorithms.

ABBREVIATIONS AND ACRONYMS

ACMG = American College of Medical Genetics and Genomics

ACS = acute coronary syndrome

CHD = coronary heart disease

DLC = Dutch Lipid Clinic

DNA = deoxyribonucleic acid

FH = familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

SB = Simon Broome

VUS = variants of unknown significance