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Detection of familial hypercholesterolemia in patients from a general practice database

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Abstract

Objectives: Familial hypercholesterolemia (FH) is the most common monogenic lipid disorder associated with premature coronary heart disease. Early cholesterol-lowering therapy could effectively reduce cardiovascular disease morbidity and mortality in these patients. However, the majority of people with FH are undiagnosed, also due to low awareness and knowledge of FH in general practice, despite the high number of contacts GPs have with most of their patients which allows a systematic and effective approach to the detection of this condition. Here, we present a simple method to improve detection and to enhance awareness of FH in primary care using GP electronic health records.

Methods: We used electronic data from the Co.S. Consortium, involving more than 600 Italian affiliated GPs. Electronic data include demographic information, laboratory test results, recorded history of vascular disease and prescription of an HMG-CoA reductase inhibitor class medication. We performed a partial assessment of the Dutch Lipid Clinic Network (DLCN) score using those data that were recorded or available. We also sought to determine the prevalence of possible FH based on age-specific LDL-cholesterol thresholds employed by the diagnostic criteria of MEDPED and the non-age adjusted cut-off point (LDL-C $\geq$190 mg/dL).

Results: Data on LDL-C were available for 162,864 subjects. Mean LDL-C levels (SD) were 124.3 (33.6) mg/dL for non-treated subjects and 106.4 (38.5) mg/dL for statin-treated subjects. The cut-off of LDL-C $\geq$190 mg/dL yielded a prevalence of 2.9% among non-treated subjects and of 3.5% among statin-treated patients. Using the cut-off of $\geq$250 mg/dL, the prevalence was 0.1% among non-treated subjects and 0.3% among statin-treated patients. Using the cut-off $\geq$330 mg/dL (suggesting a probable diagnosis of FH according to the DLCN score) the prevalence was 0.01% and 0.02%. According to the stratification proposed by MEDPED criteria for the general population, the age-specific LDL-cholesterol thresholds identified 0.7% among non-treated subjects and 18.5% among statin-treated patients.

Conclusion: The diagnosis of FH is possible in general medicine and should be an integral part of the GP's activity.

Keywords: Cardiovascular diseases; Familial hypercholesterolemia; Primary healthcare

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1. Introduction

Plasma cholesterol levels are controlled by genetic and environmental factors. Primary or familial dyslipidemias are inherited diseases caused by a single genetic mutation in one of several genes. Genetic abnormalities that lead to abnormal blood lipid levels are mainly found in genes involved in the transportation and cellular uptake of lipids. Individuals who have these mutations often have severely abnormal blood lipid levels, which results in early-onset cardiovascular disease [1].

One of the most frequent forms is familial hypercholesterolemia (FH), an inherited disease in which genetic alteration results in the increase of low-density lipoprotein cholesterol (LDL-C) levels [2]. The frequency of heterozygous FH is estimated at about 1:200−1:250 in the general population [3−6], resulting in one of the most common monogenic disorders. The homozygous form (HoFH) is very rare, with an estimated rate of 1:1,000,000 people [7]. Individuals with heterozygous FH (HeFH) have total cholesterol and LDL-C plasma levels between 300 and 500 mg/dL (7.75−13 mmol/L). In HoFH, these levels are significantly higher (600−1200 mg/dL; 15.5−31.0 mmol/L).

Early diagnosis of FH is crucial because the disease should be early treated with lipid-lowering therapy and lifestyle changes to prevent cardiovascular complications [8,9]. In Italy, it has been estimated that <1% of cases are actually recognized and there is a general lack of uniform public health initiatives specifically directed to close the gap of knowledge on FH [5].

The frequency and clinical significance of these conditions justify a major effort to identify affected individuals and their families, a task entrusted almost entirely to general practitioners (GPs). In fact, the high number of contacts by GPs with most of patients allows a systematic and effective approach to the detection of this condition [10]. In a context where systematic screening is not applied, in addition to cascade screening after the identification of an index patient, opportunistic screening through the routinely clinical practice is the only opportunity to identify FH patients. Here, we present a simple method to improve detection and to enhance awareness of FH in primary care using GP electronic health records (GP EHR).

2. Methods

We used electronic data from the Consorzio Sanità − Co.S. (see Appendix). Data were collected by more than 600 Italian GPs affiliated with the Consortium, who in their daily clinical practice periodically extracted data which, after anonymization, were collected in the "My Search" database.

Electronic data include demographic information, laboratory test results, recorded history of vascular disease and prescription of an HMG-CoA reductase inhibitor class (statin) medication.

We performed a partial assessment of the Dutch Lipid Clinic Network (DLCN) score using those data that were recorded or available. The DLCN score includes assessment of: raised cholesterol and LDL-C concentrations, clinical characteristics (such as peripheral vascular disease; coronary artery disease), presence of tendon xanthoma or arcus cornealis, and a family history of premature heart disease [11]. The data extracted did not contain family history or examination findings, therefore the partial DLCN score assessment only included LDL-C concentrations and, where recorded, a personal history of vascular disease. The score determines the likelihood of an FH diagnosis as unlikely (<3 points), possible (3−5 points), probable (6−8 points), or definite (>8 points) FH.

We also sought to determine the prevalence of possible FH based on age-specific LDL-cholesterol thresholds employed by the diagnostic criteria of MEDPED [12] and the non-age adjusted cut-off point (LDL-C ≥190 mg/dL) adopted by the Italian Medicines Agency (AIFA) to regulate reimbursement of lipid lowering drugs in Italy, together with personal or familial history of premature coronary artery disease or tendinous xanthomata.

Descriptive statistics were calculated to describe patient characteristics. All analysis and results were completed in IBM SPSS Statistics version 23.

3. Results

Data on LDL-C were available for 162,864 subjects. Among them, 22.9% were on statin treatment. Mean LDL-C levels (SD) were 124.3 (33.6) mg/dL for non-treated subjects and 106.4 (38.5) mg/dL for statin-treated subjects. The serum LDL-C distribution for non-treated and statin-treated subjects is shown in Fig. 1A and B, respectively. The median serum LDL-C concentrations were 123.4 mg/dL. The 95th and 99th percentiles for serum LDL-C were 180.4 and 207.8 mg/dL, respectively.

The cut-off adopted by the Italian Medicines Agency of LDL-C ≥190 mg/dL yielded a prevalence of 2.9% among non-treated subjects and of 3.5% among statin-treated patients. Importantly, this last value is likely to be underestimated, as calculated on LDL-C levels reduced due to the lipid-lowering therapy. Assuming an average 30% reduction in LDL-C achieved by statin therapy and back-calculating hypothetical pre-treatment levels, the application of this cut-off would identify 20.8% of treated subjects (7.0% of the total sample).

If we considered the most recently estimated prevalence of FH in the general population of 1:200−1:250 [13], the cut-off of LDL-C in this population of untreated subjects would be 218 and 222 mg/dL, respectively.

The cut-off of 190 mg/dL also corresponds to the lowest threshold for the stratification of the levels of LDL-C

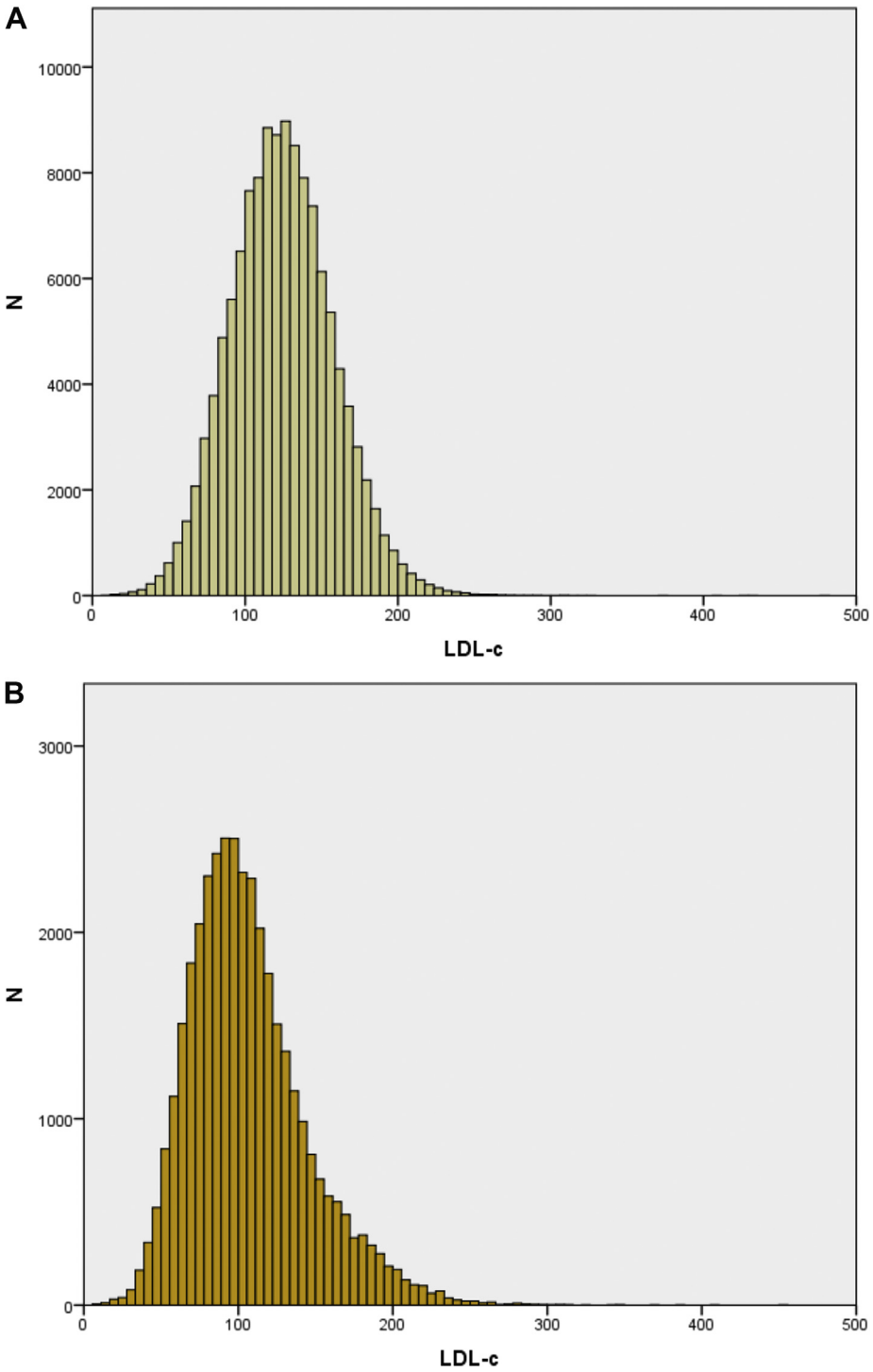

Fig. 1. **A**. Plasma LDL-cholesterol distribution of non-treated subjects (N = 125,609). **B**. Plasma LDL-cholesterol distribution of statin-treated subjects (N = 37,254).

according to DLCN score; in particular, this criterion gives 3 points for the clinical diagnosis of FH.

Using the next cut-off (≥250 mg/dL), which gives 5 points according to the DLCN score, the prevalence was 0.1% among non-treated subjects and 0.3% among statin-treated patients. Using the cut-off ≥330 mg/dL, which gives 8 points according to the DLCN score, i.e. a probable diagnosis of FH, the prevalence was 0.01% and 0.02%, respectively. According to the stratification proposed by MEDPED criteria for the general population, the age-specific LDL-cholesterol thresholds identified 0.7% among non-treated subjects and of 18.5% among statin-

Table 1
Potential FH prevalence based on DLCN score.

	Non-treated subjects		Statin-treated patients	
	Number of people meeting the criteria	Prevalence	Number of people meeting the criteria	Prevalence
≥190 mg/dL (possible FH)	3651	1:34	1291	1:29
≥250 mg/dL (probable FH)	121	1:1038	101	1:369
≥330 mg/dL (probable FH)	7	1:17,944	8	1:4657

Table 2
Potential FH prevalence based on MEDPED criteria.

	Number of people meeting the criteria	
	Non-treated subjects	Statin-treated patients
Age <20 years, LDL-cholesterol ≥200 mg/dL	3	0
Age 20–29 years, LDL-cholesterol ≥220 mg/dL	7	2
Age 30–39 years, LDL-cholesterol ≥240 mg/dL	17	6
Age ≥40 years, LDL-cholesterol ≥260 mg/dL	64	61
Total	91	69
Prevalence	1:1380	1:540

treated patients. The number of subjects and prevalence using the MEDPED criteria and the DLCN criteria are shown in Tables 1 and 2, respectively.

4. Discussion

Familial hypercholesterolemia is an autosomal genetic disease, characterized by elevated lipid levels and a severe and early onset of coronary heart disease. Affected subjects are therefore at high cardiovascular risk and need to be identified as early as possible in order to establish effective preventive treatments.

Commonly, however, the recognition of FH is far below the expected [5]. This is particularly crucial because of the high CV risk of young or relatively young persons, who would be at low risk on the basis of traditional charts or algorithms.

In the current practice of general medicine, the identification of family forms can be only opportunistic (that is, as a result of contacts required by the patient for various reasons), since the active screening procedures are still not compatible with the available resources. This means that GPs have a great diagnostic potential [14,15]: the high number of contacts with most of the population assisted by the GP in a few years allows a systematic and effective approach to this problem, simply applying what is already recommended by the guidelines as normal good clinical practice.

The cut-off of 190 mg/dL for LDL-C would be a first screening. The prevalence found in the population in this study means that, on average, a GP would identify about 30 individuals per 1000 patients. Then, the diagnosis should be based on the deepening of the patient's personal and family pathological history and on a clinical examination aimed to detect the presence of any signs of illness, such as xanthomas, xanthelasma, or non-senile arcus cornealis. Prevalence data published so far suggest that, on average, each doctor might find 2–5 FH subjects per 1000 patients [5].

The clinical diagnosis should be confirmed in the genetic analysis of candidate genes, searching for causative mutations [16]. The high levels of LDL-C in FH subjects are due to an absent or reduced removal of LDL from the bloodstream, which may be due to a deficiency of synthesis or to an altered function of the LDL receptor (LDLR), caused by mutations in the gene encoding the LDL receptor or other molecules involved in its metabolism [16]. Moreover, to identify a causative mutation means being able to make a definitive diagnosis, excluding secondary hypercholesterolemia and to distinguish between the classical FH due to LDLR mutations and the other genetic causes of FH. Notably, many clinically diagnosed FH patients fail to show any mutation in the candidate genes [17,18]. This diagnostic gap could be explained by mutations in other unknown novel genes that are involved in cholesterol metabolism but, most probably, by an accumulation of common small-effect LDL-C-raising alleles. As a result, a substantial proportion of the raised LDL-C concentrations in patients with a clinical diagnosis of FH with no detected causative mutation have a polygenic rather than a monogenic cause [19]. For these individuals (and their relatives), the absence of mutation as from genetic analysis does not mean absence of disease: the signs and symptoms of the disease, primarily the high LDL-C levels, should be the target of a specific therapy.

Given the hereditary transmission of the disease, the cascade screening of relatives should follow the identification of an affected person (index patient) [14,20]. In fact, it is important to underline that, in most cases, the GP has to manage an entire family unit, so that effective communication with all family members is a key point to make patients more conscious of their condition, in order to encourage changes in lifestyle and improve adherence to drug treatment.

The relatively asymptomatic nature, at least until the development of coronary heart disease, and its epidemiological frequency make FH a preferential target for the general practitioner. Using the lipid profile as a starting point and taking advantage of the software for the

management of clinical data now available to general practice, GPs can easily select a small group of patients for further assessment to early diagnose the disease and, as applicable, initiate or strengthen the lipid-lowering therapy as soon as possible. The diagnosis of FH is therefore possible within general medicine and should be integral part of the GP's activity, also because GPs are in the best position to identify patients before they manifest CV events.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix

Consorzio Sanità (Co.S.) was founded in 1997 and it is a national group of 29 cooperatives, which have more than 2300 General Practitioners (GPs) as members, assisting more than 2.6 million citizens across 10 Italian regions (Lombardy, Veneto, Emilia-Romagna, Liguria, Toscana, Lazio, Campania, Abruzzo, Calabria and Sicilia).

Co.S.'s mission is to build a framework for integrated services for AFT/UCCP groups, within a multi-professional (both Medical and Social services), cooperative organization which focuses on comprehensive care-taking paths for chronic and fragile patients.

Co.S. Centro Studi (research center) http://www.centrostudicos.org/

Individual GPs and cooperatives take part in *Centro Studi Co.S. (Co.S. research center)*, whose goal is to study, define and implement specific projects that align with Co.S.'s mission, in the following areas:

- *Epidemiological studies:*
  - Prevalence studies (especially for chronic conditions)
  - Identification of risk factors: cardiovascular conditions, diabetes, cancer…
- Observational studies:
  - "Natural" trends for major chronic conditions, with assessment of the related end points
  - Assessment of efficacy of pharmaceutical treatments, as well as lifestyle counselling, towards reducing intermediate outcome indicators
- *Projects aimed at prevention and well-being:*

Centered on correlation between obesity and diabetes, smoking and lung cancer, fitness and cardiovascular conditions…

- Clinical Governance:

Analysis of performance indicators, both professional and organizational, in managing care-taking paths for chronic and fragile patients, for an adequate reallocation of resources.

"My Search" database

Practitioners joining the *Centro Studi* submit at least monthly data they produce in their daily clinical practice. This data is sent from their electronic medical record software to *Centro Studi*, without any limitation on the type of electronic medical record software they use. The *Centro Studi* software framework is based on an interoperability tool, OSM-Connector®, which can extract data from any electronic medical record software and, after anonymization; it creates a standard XML record (shared across multiple SW vendors) which it sends via a VPN tunnel to *Centro Studi*.

The *Centro Studi* Database Management System is MariaDB, which is a MySQL fork running in Linux. This is a free software database; it is open to dialogue with the community and focuses on a good interoperability with other softwares, a philosophy aligned with Co.S.'s own.

As of writing (Nov 2016), 602 GPs contribute to the *My Search* database, covering 871,634 citizens

"My Search" portal

The portal allows GPs to run predefined queries, which offers them a powerful tool to perform:

- *Self-Auditing,* with possibility to receive coaching from his/her co-op to reach his/her prescription appropriateness goals, as agreed with Local Health Authority
- *Pathology Records,* to monitor prevalence of major chronic conditions (including a geographic epidemiology map)
- *Clinical Governance,* analysis of professional performance indicators in managing care-taking paths to manage chronicity
- *Continuous Quality Improvement,* elaboration of specific process and outcome indicators, aimed at continuous quality improvement

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