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Treatment pattern of familial hypercholesterolemia in Slovakia: Targets, treatment and obstacles in common practice

Branislav Vohnout [a, b, *], Ľubomíra Fábryová [c], Alexander Klabník [d], Michaela Kadurová [e], Karin Bálinth [f], Miriam Kozárová [g], Ingrid Bugáňová [h], Jana Sirotiaková [f], Katarína Rašlová [b]

[a] Institute of Nutrition, Faculty of Nursing and Professional Health Studies, Slovak Medical University in Bratislava, Limbová 12, 833 01, Bratislava, Slovakia
[b] Co-ordination Center for Familial Hyperlipidemias, Faculty of Public Health, Slovak Medical University in Bratislava, Slovakia
[c] Metabolklinik Ltd, Bratislava, Slovakia
[d] Cardiology Clinic, Námestovo, Slovakia
[e] Lipid Clinic, Poprad, Slovakia
[f] Dept. of Internal Medicine, Hospital Levice, Slovakia
[g] IVthDept. of Internal Medicine, Medical Faculty, PJ Šafárik University, Košice, Slovakia
[h] Diabetes Clinic, MEDIVASA Ltd, Žilina, Slovakia

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ABSTRACT

Background and aims: Maximal doses of potent statins are the cornerstone of treatment of familial hypercholesterolemia (FH). Despite this, a substantial proportion of FH patients are either under-treated or not treated at all. The aim of this work was to evaluate, in a retrospective study, the treatment of FH patients, the proportion of FH patients reaching low-density lipoprotein cholesterol (LDL-C) goals, and reasons for not reaching LDL-C goals, in 8 lipid clinics in Slovakia dealing with FH patients.
Methods: 201 heterozygous FH patients (50.8 ± 14.9 years, 55% females) who attended the lipid clinics at least three times were included in the study.
Results: At the first visit, 31.3% of patients were treated with statins and the most common dose was 20 mg of atorvastatin, rosuvastatin and simvastatin. At the third visit, 78.1% of patients were treated with statins and 24.4% with ezetimibe. The majority of patients were treated with atorvastatin (75.8%) and rosuvastatin (18.5%) and 31.3% of all patients were treated with atorvastatin 80 mg or rosuvastatin 40 mg with/without ezetimibe. However, only 11.9% of patients with the LDL-C goal level <2.5 mmol/l and 6.9% with the goal <1.8 mmol/l reached the level. Reasons for not reaching the goal levels were evaluated by physicians in each patient. Insufficient LDL-C lowering effect of treatment, side-effects of therapy and non-compliance of patients were responsible for 46%, 18% and 30% of cases, respectively.
Conclusions: Referral of FH patients to lipid clinics in Slovakia leads to improvement in the treatment; however, almost 22% of the patients are still without statin treatment and the majority of patients do not reach the LDL-C goal level.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder that occurs in the heterozygous form in approximately 1 in 200–500 individuals, with more recent estimates of 1:250 from systematic review and meta-analysis of different studies [1,2]. The disease is characterised by strikingly elevated LDL-cholesterol, the presence of xanthoma, and premature atherosclerosis. Heterozygous FH show low-density lipoprotein cholesterol (LDL-C) levels in the range 5–10 mmol/l and, if left untreated, typically develop coronary heart disease (CHD) before the age of 55 in men and 60 years in women [1]. However, once diagnosed, they can readily be treated with cholesterol-lowering medication to attenuate development of atherosclerosis and to prevent coronary heart disease [3,4]. Despite the fact that cholesterol-lowering treatment with a maximal potent statin dose

* Corresponding author. Institute of Nutrition, FOaZOS, Slovak Medical University in Bratislava, Limbová 12, 833 01, Bratislava, Slovakia.
E-mail address: bvohnout@yahoo.com (B. Vohnout).

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Table 1
Main characteristics of patients.

Age	50.8 ± 14.9 years
Sex (females/males)	55%/45%
Diabetes	10.5%
FH diagnosis	
Genetic	48.2%
Dutch Lipid Clinic Network criteria	32.7%
Simon Broome Register criteria	11.6%
US MED PED criteria	7.5%

Mean±SD.
FH diagnosis: proportion (%) of the FH patients confirmed genetically or with clinical diagnosis only (Dutch Lipid Clinic Network, Simon Broome or US MedPed criteria).

should be initiated immediately at the time of diagnosis, results of a few cohort studies suggest that many FH patients receive insufficient statin doses and many physicians do not up-titrate statin doses to reach the LDL-C goal levels [3–5].

Diagnosis and treatment of FH patients in the Slovak republic were first performed in 1999 as part of the MedPed FH Slovakia project [6,7]. A network of MedPed FH collaborating out-patient departments serve as referring departments for general practitioners and specialists not focused on lipid disorders. All three major clinical criteria (the Dutch Lipid Clinic Network (DLCN), the Simon Broome Register and US MED PED criteria) have been used to establish clinical diagnosis of FH; however, currently, the DLCN criteria are preferentially used [8–10]. Recently, genetic testing has become partially available due to scientific projects and health care insurance [11]. Lipid-lowering therapy and health care are available in Slovakia for free or with only marginal financial participation of the patients.

The aim of the current study was to evaluate everyday clinical practice in the management of FH patients and to identify obstacles related to proper treatment of FH in 8 busy out-patient departments involved in the MedPed FH project in Slovakia. In particular, we were interested in the proportion of patients reaching LDL-C goal levels according to the EAS/ESC 2011 treatment guidelines [12] and in the proportion of FH patients under maximal doses of potent statins.

2. Patients and methods

Patients with definite or probable diagnosis of FH (using all three major clinical criteria - DLCN, the Simon Broome Register and US MED PED criteria, according to preferences of the participating centres) were included in this retrospective observation in 8 MedPed FH centres (four Diabetes Clinics, three Internal Medicine Departments and one Cardiology Centre) geographically distributed throughout Slovakia. Other inclusion criteria were age ≥18 years, signed informed consent to participate in the MedPed FH project, and individual patients medical records from at least 3 clinical visits in a centre, of which at least one was performed in 2015. Data collection was performed between December 2015 and January 2016. A minimum of 3 clinical visits was required to ensure sufficient possibility to initiate and/or up-titrate statin therapy for optimal treatment. FH diagnosis was confirmed by the presence of mutations in the LDL receptor or APOB genes [11] in 48.2% of the patients; in the remaining patients, the diagnosis was based on clinical diagnosis only. Data from the first patients visit in the centre and from the last visit in 2015 were retrospectively collected using a structured questionnaire. The information collected included lipid levels, type and dose of lipid-lowering therapy, personal history of diabetes, myocardial infarction, stroke, peripheral artery disease, percutaneous coronary intervention and coronary artery bypass surgery. Emphasis was given to obtaining information as to whether LDL-C goal levels were reached at the last visit, and reasons for not reaching it were evaluated by physicians by choosing one or more predefined options (not sufficient lipid-lowering therapy effect, side effect of the therapy - e.g. myopathy or intolerance due to other reasons, bad compliance of a patient with therapy, cost of treatment paid by a patient or other reason). Serum LDL-C concentration was calculated using the Friedewald formula [13]. The MedPed FH Slovakia project was approved by the central ethics committee, and all subjects gave written informed consent.

Quantitative data were expressed as mean and standard deviation (SD) and qualitative data as absolute number and percentage. Comparisons of frequencies between qualitative variables were carried out using the chi-square test or Fisher exact test. Normal distributions of quantitative variables were examined by using the Shapiro-Wilk W test for normality. Differences between the measured quantitative parameters were compared by paired *t*-test or Wilcoxon signed-rank test based on distribution of data.

3. Results

Two hundred and one FH patients (mean age 50.8 ± 14.9 years, 111 females - 55% and 90 males - 45%) were included in the study (Table 1). Prevalence and mean time of occurrence (first occurrence in case of more events in the same patient) of myocardial infarction, stroke and peripheral artery disease were 13.4% (51.3 ± 11.7 years), 3% (60.0 ± 12.2% years) and 4% (51.2 ± 3.8 years), respectively. Percutaneous coronary intervention and coronary artery bypass surgery were done in 10.4% (51.9 ± 9.5 years) and 6.5% (60.2 ± 9.0 years) of FH patients. Prevalence of diabetes was 10.4%.

The main characteristics of lipid levels and statin treatment are listed in Table 2. At the first visit to centres, 31.3% of patients were treated with statins (37.3% on any lipid lowering therapy, e.g. statins, ezetimibe, fibrates, resins) and the most common dose was 20 mg of a potent statins (given to 59% of those patients receiving

Table 2
Main characteristics of lipids and treatment.

	Initial visit	Last visit
Total cholesterol [mmol/l]	8.3 ± 1.4	6.0 ± 1.6[a]
LDL-C [mmol/l]	6.0 ± 1.4	3.9 ± 1.5[a]
HDL-C [mmol/l]	1.4 ± 0.5	1.5 ± 0.6
Triglycerides [mmol/l]	1.6 ± 0.7	1.4 ± 0.7[a]
Statin treatment	31.3%	78.1%[a]
Any hypolipidemic treatment	37.3%	78.6%[a]
Atorvastatin [% of all statins, mean dose]	61.9%, 33.6 ± 21.8 mg	75.8%[a], 51.0 ± 26.7 mg[a]
Rosuvastatin [% of all statins, mean dose]	11.1%, 22.9 ± 12.5 mg	18.5%[a], 27.7 ± 13.1 mg[a]
Simvastatin [% of all statins, mean dose]	20.6%, 23.8 ± 9.6 mg	3.8%[a], 27.5 ± 14.7 mg
Fluvastatin [% of all statins, mean dose]	4.8%, 66.7 ± 23.1 mg	1.9%[a], 80 mg[a]

[a] $p < 0.05$, p for before *vs*. after management in the MedPed centres; mean ± SD.