EDITORIAL

Management of familial heterozygous hypercholesterolemia

Position paper of the Polish Lipid Expert Forum

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Introduction Familial hypercholesterolemia (FH) is one of the better-known genetically determined diseases causing an accelerated development of atherosclerosis and early occurrence of cardiovascular events.[1-3] Symptoms of coronary heart disease develop in more than half of men with heterozygous FH (HeFH) before the age of 50 years and in 30% of women before the age of 60 years. Cardiovascular mortality in individuals with FH between 20 and 39 years of age is 100-times higher than in the general population.[1] Early identification of individuals with HeFH and effective pharmacotherapy may decrease the incidence of cardiovascular events and reduce premature mortality.[4,5] Unfortunately, the majority of patients affected by HeFH in Poland are unaware of the disease.

Epidemiology and pathogenesis FH is the most common monogenetic disease.[1,6] Due to the autosomal dominant inheritance, there are heterozygous (HeFH) and homozygous (HoFH) forms of the disease. HoFH occurs in 1 per 1 million live births, while HeFH affects on average 1 in 500 individuals in the European countries.[1] It is estimated that HeFH in Poland may affect more than 80,000 people.

The phenotype of FH is associated with the mutation of 1 of the 3 genes: low-density lipoprotein (LDL) receptor gene (approx. 1600 different mutations were described), apolipoprotein B (*apoB*) gene or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene.[7-10] Abnormal structure of LDL receptors or *apoB*, the ligand for LDL receptors, disturbs the binding of *apoB* containing lipoproteins to receptors. This results in impaired catabolism of LDL in the liver.[11,12] In HeFH, the defect affects half the LDL receptors or half the *apoB* molecules. The third, recently discovered cause of FH is the presence of *PCSK9* gene mutation, which is associated with the degradation activity of LDL receptors by this protein (gain-of-function mutation).[10,13]

Familial hypercholesterolemia as a risk factor for coronary heart disease FH is a potent risk factor of coronary heart disease.[14] The coexistence of additional risk factors, especially smoking, significantly accelerates the development of premature atherosclerosis.[1,3] It is estimated that in the majority of untreated men and women with HeFH, coronary heart disease manifests itself before the age of 60 years. FH patients are a priori assigned to the high-risk group without the need to use the European Society of Cardiology (ESC) Heart Score or Framingham algorithm to estimate the cardiovascular risk in the primary prevention. Early implemented intensive pharmacotherapy before the appearance of atherosclerosis symptoms allows to achieve life expectancy among the individuals with HeFH similar to the general population.[15-17]

Heterozygous familial hypercholesterolemia diagnostic criteria FH is diagnosed on the basis of the Dutch Lipid Network criteria adopted in Geneva in 1998 by the World Health Organization.[1] The criteria were also adopted by the ESC and European Atherosclerosis Society (EAS) in "ESC/EAS Guidelines for the Management of Dyslipidaemias" 2011.[3] The clinical criteria of FH include high plasma levels of LDL cholesterol, presence of arcus cornealis and tendinous xanthomas, premature cardiovascular disease, and positive family history of hypercholesterolemia and premature cardiovascular disease. [6,18,19] The presence of xanthomas on the extensor tendons of the hands and on the Achilles tendon is pathognomonic for the diagnosis of FH. The lower age limit for premature cardiovascular disease is considered to be 55 years in men and 60 years in women.

The basic biochemical parameter in FH diagnosis is the high level of LDL cholesterol (in heterozygotes usually from 2 to 3 times higher than the population average), usually with a normal level of triglycerides.[1,16] Total cholesterol level in heterozygotes is usually between 290 and 500 mg/dl (7.5–12.9 mmol/l), and in homozygotes between 600 and 1000 mg/dl (15.5–25.8 mmol/l).[1] Lipid profile in patients with FH may resemble that obtained in secondary hypercholesterolemia, e.g., in the course of hypothyroidism, diabetes, nephrotic syndrome, as a result of long-term therapy with corticosteroids, progestogens, or protease inhibitors used to treat human immunodeficiency virus infection.[3] Sometimes, an increased level of triglycerides secondary to, for example, diabetes, obesity, or excessive alcohol consumption occurs in typical FH. In such cases, any doubts about the diagnosis of FH can be clarified by obtaining a lipid profile of relatives and by genetic testing.[19]

The Dutch Lipid Network and Simon Broome Register criteria adapted to Polish conditions (TABLE) may be helpful in the office setting. They allow to make a certain, probable, or possible diagnosis of FH in the clinical setting.[1-3] It should be noted that the clinical diagnosis of FH might be established without genetic testing.[19] If financially feasible, it is advisable to confirm FH diagnosis by genetic methods, especially in doubtful cases.

Adapted Dutch Lipid Clinic Network and Simon Broome Register diagnostic criteria for HeFH are presented in the TABLE.

Recommendations for identification of heterozygous familial hypercholesterolemia According to the National Institute for Health and Clinical Excellence (NICE) guidelines, coexistence of cholesterol concentration over 300 mg/dl (7.8 mmol/l) with premature cardiovascular disease in first-degree relatives (siblings, parents, or children) is strongly suggestive of FH.[2,20] In families with FH, the condition should be diagnosed in children and dietetic treatment initiated as soon as possible; treatment with statins should be introduced in children over 10 years of age.[21] If HeFH is diagnosed, cascade screening of the family is recommended, including both serum lipid profile and genetic testing (if possible). [1,2,22]

The measurement of serum lipid concentration in children in families with FH is recommended even immediately after birth and always under 10 years of age. Children in such families should undergo periodic medical examinations, including the measurement of body weight and blood pressure.[21]

Atherosclerosis in FH develops insidiously and may be advanced before any signs or symptoms are noted. Markers of coronary heart disease may be present in asymptomatic patients.[23] Specialist care for patients with FH makes it possible to confirm the diagnosis of FH in dubious cases using a genetic method, introduce cascade testing in the families, and recommend lifestyle modifications and pharmacotherapy.[22,24,25] It is necessary to provide patients with a quick access to diagnostic tests, which allows to detect significant cardiovascular disease and, if possible, cooperate with clinical geneticist. National programs for patients with FH are in place worldwide: MEDPED in the United States, StOEH in the Netherlands, HEART UK – The Nation's Cholesterol Charity in England, Fundacion Colesterol Familiar in Spain, Krajowe Centrum Diagnostyki Hipercholesterolemii Rodzinnej (National Centre for Diagnostics of Familial Hypercholesterolaemia) in Poland, and others. It must be stressed that there are no separate lipid clinics in the Polish healthcare system.

Target low-density lipoprotein cholesterol concentration After clinical diagnosis of FH has been established (a score of 5 or more), intensive treatment should be initiated without waiting for the results of molecular testing.[2-5]

The target LDL cholesterol concentration in patients with FH in primary prevention of coronary heart disease, due to a high risk, should be less than 2.5 mmol/l (<100 mg/dl). In patients with

TABLE Heterozygous familial hypercholesterolemia diagnostic criteria – score; adaptation of the Dutch Lipid Clinic Network (World Health Organization) and Simon Broome Register scale

clinical history		
premature coronary heart disease (men <55 years, women <60 years)		2
premature cerebral or peripheral vascular disease		1
family history		
first-degree relatives with premature coronary or vascular disease		1
first-degree relatives with LDL above 190 mg/dl		1
first-degree relatives with tendon xanthomata and/or corneal arcus		2
children aged less than 18 years with LDL cholesterol above 155 mg/dl		2
physical examination		
tendon xanthomata		6
corneal arcus below the age of 45 years		4
laboratory analysis		
LDL cholesterol	>8.5 mmol/l (330 mg/dl)	8
	6.5–8.4 mmol/l (250–329 mg/dl)	5
	5.0–6.4 mmol/l (190–249 mg/dl)	3
	4.0–4.9 mmol/l (155–189 mg/dl)	1
genetic testing		
mutation of LDL receptor gene		8
diagnosis of familial hypercholesterolemia		
definite		>8
probable		6–8
possible		3–5
no diagnosis		<3

Abbreviations: LDL – low-density lipoprotein

concomitant cardiovascular disease the risk is very high and the goal of treatment is LDL cholesterol concentration below 1.8 mmol/l (<70 mg/dl).[2,5] If this is not possible, reduction by at least 50% from baseline is recommended. This goal may be difficult to achieve with statins alone; therefore, combination pharmacotherapy is often necessary.[3] In the ESC/EAS guidelines on the management of dyslipidemia (2011) the experts stated: "if the target level is not reached, statin combination with cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered". In Poland, only the first option is currently feasible, i.e., the addition of ezetimibe after an attempt at treatment with the maximum tolerated dose of a statin, is feasible.

In our opinion, a score of 5 or more should be considered sufficient justification for the introduction of the recommended treatment of FH, reimbursed from the public means in Poland.

Therapeutic management of heterozygous familial hypercholesterolemia The most important objective of treatment in patients with FH is to reduce premature cardiovascular mortality as well as the incidence of myocardial infarction and the need for revascularization. Lifestyle changes are necessary to eliminate additional cardiovascular risk factors.[3] Recommendations for patients with FH include absolute abstinence from smoking, physical activity (at least 30 minutes of exercise for a minimum of 5 days per week – brisk walking, running, or cycling), arterial blood pressure <140/90 mmHg, body mass index <25 kg/m^2, avoidance (or treatment) of central obesity, and cholesterol-lowering diet.[1-3] However, in patients with FH even an appropriate diet would not adequately lower the LDL cholesterol concentration, and the introduction of pharmacological treatment is necessary. In FH, the treatment of choice are statins at the maximum tolerated dose.[3,18] Response to treatment with statins is highly individually variable (concentration reduction by 10% to 70%) due to (among other factors) the type of the LDL receptor mutation. Although statins are currently the most potent class of hypolipemic medications available, in many patients with FH (as mentioned above) the target LDL cholesterol concentrations cannot be achieved with monotherapy.[2,3,18,25] In such cases, the goal of treatment should be the maximum LDL cholesterol reduction attainable with an appropriate combination treatment at tolerated doses: a statin with a cholesterol absorption inhibitor (ezetimibe), a bile acid-binding agent (anion-exchange resin), or nicotinic acid.[3] In the case of statin intolerance, ezetimibe, an anion-exchange resin or nicotinic acid may be used in monotherapy. A modern anion-exchange resin (colesevelam) and nicotinic acid are not yet available in Poland. The position concerning treatment of children and adolescents will be presented in a separate paper.

Women with FH who plan pregnancy or are pregnant or breastfeeding should not receive statins.[26] In women of childbearing potential, the use of highly effective contraceptive methods is recommended; oral hormonal contraceptives should be avoided, if possible. Women should be instructed to stop hypolipemic treatment 3 months prior to the planned pregnancy.[26] The only hypolipemic treatment admissible in pregnancy is the use of an agent preventing the enterohepatic recirculation of bile acids (e.g., colesevelam).

A new class of medications, PCSK9 inhibitors, may offer a promising treatment option in FH, and the results of studies concerning these drugs (published in 2012) indicated that the hypolipemic effect of the investigated monoclonal antibodies was convincing.[27-32]

Conclusions HeFH is a relatively common lipid disorder, usually remaining undiagnosed and untreated. A very high risk of cardiovascular diseases and a shortened lifespan in patients with this condition require early diagnosis and intensive treatment.

Note The position paper has been officially endorsed by the Cardiovascular Working Group of the Polish Cardiac Society.

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Krka, MSD, Novartis, Pfizer, Polpharma, Teva); T.G.: honoraria (Bayer); P.J.: honoraria for lectures/travel funds (Abbot, Adamed, AstraZeneca, MSD, Polpharma, Sanofi-Aventis, Zentiva); G.O.: clinical trials/lectures (Adamed, AstraZeneca, Egis, Krka, MSD, Novartis, Pfizer, Polpharma, Teva); J.S.: honoraria for lectures/membership in advisory boards (Adamed, AstraZeneca, Bristol-Myers Squibb, Egis, MSD, Novartis, Pfizer, Polpharma).

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