NEW IN 2016, UPDATE OF POLISH FORUM FOR PREVENTION GUIDELINES ON DYSLIPIDAEMA

1. New data on epidemiology of dyslipidaemia in the Polish population
2. New treatment goals for low-density lipoprotein cholesterol (LDL-C) in high- and very high-risk groups
3. Indications for the use of inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9)
4. Assessment of alanine aminotransferase (ALT) and creatine kinase (CK) before starting statins
5. No need for routine monitoring of ALT and CK during statin therapy

1. DYSLIPIDAEMA — DEFINITION

The characteristic feature of dyslipidaemia is abnormal concentration of one or more lipoprotein fractions or their composition in serum in the fasting state. In clinical practice, dyslipidaemias are defined on the basis of the laboratory test results [1–3]:

— hypercholesterolaemia — total cholesterol concentration (TC) ≥ 5.0 mmol/L (≥ 190 mg/dL) and (or) LDL-C concentration ≥ 3.0 mmol/L (≥ 115 mg/dL);
— hypertriglyceridaemia — triglyceride concentration (TG) ≥ 1.7 mmol/L (≥ 150 mg/dL); severe hypertriglyceridaemia is defined as triglyceride concentration > 10 mmol/L (> 900 mg/dL);
— low high density lipoprotein cholesterol (HDL-C) concentration < 1 mmol/L (< 40 mg/dL) in men and < 1.2 mmol/L (< 45 mg/dL) in women;
— mixed hyperlipidaemia — increased LDL-C and TG levels with frequently decreased HDL-C level.

2. ETIOPATHOGENESIS OF DYSLIPIDEMIA
Primary dyslipidaemia is usually caused by environmental factors (such as unhealthy diet, low physical activity, smoking) and genetic predisposition. Primary dyslipidaemia also includes heterozygous familial hypercholesterolaemia (FH) characterised by a prominent tendency to develop premature atherosclerosis (it can be suspected if the concentration of TC is ≥ 320 mg/dL) [2].

Secondary dyslipidaemia may occur in hypothyroidism, cholestatic jaundice, primary biliary cirrhosis, kidney disease, obesity, diabetes, multiple myeloma, bulimia, and lipodystrophy and when using corticosteroids, immunosuppressing drugs, and oestrogens, especially oral, cyclosporine, some beta-blockers, thiazide diuretics, protease inhibitors, and retinoids [2, 3].

3. EPIDEMIOLOGY
In the Polish adult population (age ≥ 20 years) hypercholesterolaemia occurs in 70% of men and in 64% of women (67% on average). Most of them (61%) are not aware of having the condition, and an additional 17% are aware but are not treated for it. Only 6% are treated and reach the treatment target. Additionally, hypertriglyceridaemia with normal concentration of TC occurs in 6% of men and in 2% of women, and low levels of HDL-C in persons with normal TC and TG occurs in 5% and 7%, respectively. In total, 77% of the Polish adult population (proximately 23.5 million) have one or more forms of dyslipidaemia, which increases cardiovascular risk. Although the prevalence of hypercholesterolaemia did not change significantly in the last decade, the prevalence of hypertriglyceridaemia (in men) and the prevalence of low HDL-C (both sexes) increased, reflecting unfavourable lifestyle changes in Polish adults [4].

4. CARDIOVASCULAR DISEASE RISK
Cardiovascular disease (CVD) risk is increased in hypercholesterolaemia, low HDL-C concentration, and to a lesser extent in hypertriglyceridaemia, which, if severe, is also a risk factor for acute pancreatitis [2]. Every 1.0 mmol/L (40 mg/dL) reduction in LDL-C is associated with a corresponding decrease in major cardiovascular events by 23%, stroke incidence by 17%, coronary disease mortality by 20%, and overall mortality by 10% [5].

5. SCREENING FOR DYSLIPIDEMIA (LIPID PROFILE)
Lipid analysis is recommended along with the evaluation of other risk factors in men ≥ 40 years of age and in women ≥ 50 years of age or after menopause. Determination of lipid profile is always recommended in the case of: the occurrence of CVD, diabetes, hypertension, obesity, cigarette smoking, chronic kidney disease, chronic inflammatory disease, or a positive family history of premature occurrence of CVD and/or dyslipidaemia. In patients with acute coronary syndrome, lipid profile should be determined within the first 24 h of onset of symptoms.

6. LIPID PROFILE DETERMINATION METHODS
The test should be made from plasma or serum of venous blood taken in the fasting state, i.e. at least 12 h after the last meal [2, 4, 6]. TC, HDL-C, and TG levels are determined by the direct method. LDL-C level can be calculated on the basis of the Friedewald formula, or determined by the direct method (necessary when TG ≥ 4.5 mmol/L, i.e. ≥ 400 mg/dL). Evaluation of chylomicronaemia (cold flotation test) should be performed if TG concentration is ≥ 10 mmol/L (≥ 900 mg/dL).

7. TREATMENT GOALS
Treatment goals must take into account the level of cardiovascular risk (refer to PFP Guidelines on the assessment of cardiovascular risk) and it is recommended to achieve appropriate levels of LDL-C (primary treatment goal), non-HDL-C, and apolipoprotein (apoB) (secondary treatment goals, in the case of hypertriglyceridaemia, metabolic syndrome, diabetes mellitus, chronic kidney disease) accordingly [2, 3].

   Treatment goals according to cardiovascular risk:
   • Very high risk
      — LDL-C < 1.8 mmol/L (< 70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 mmol/L and 3.5 mmol/L (70 mg/dL and 135 mg/dL);
      — non-HDL-C < 2.6 mmol/L (< 100 mg/dL);
      — apoB < 80 mg/dL.
   • High risk
      — LDL-C < 2.6 mmol/L (< 100 mg/dL), or a reduction of at least 50% if the baseline is between 2.6 mmol/L and 5.1 mmol/L (100 mg/dL and 200 mg/dL);
      — non-HDL-C < 3.3 mmol/L (< 130 mg/dL);
      — apoB < 100 mg/dL.
   • Low to moderate risk
      — LDL-C < 3.0 mmol/L (< 115 mg/dL);
      — non-HDL-C < 3.8 mmol/L (< 145 mg/dL).

Regardless of the degree of CVD risk, it is proposed that the following concentrations are obtained: fasting TG < 1.7 mmol/L (150 mg/dL) or < 2 mmol/L (200 mg/dL); HDL-C in men > 1.0 mmol/L (40 mg/dL), and women > 1.2 mmol/L (45 mg/dL), because these levels are associated with decreased risk [2, 3]. They are, however, not acknowledged as goal values because there is no evidence from randomised controlled trials.
In all diabetic patients ≥ 40 years of age, initiation of statin therapy is recommended (target concentration of LDL-C < 1.8 mmol/L; < 70 mg/dL).

8. NON-PHARMACOLOGICAL TREATMENT
Non-pharmacological interventions should be recommended to every patient with dyslipidaemia (Appendix 1) [2, 3]. The main recommendations include: dietary modifications, physical activity, normalisation of body weight, and tobacco abstinence.

9. PHARMACOLOGICAL TREATMENT
Pharmacotherapy should be considered when diet and lifestyle changes do not allow for the achievement of the treatment goals and alongside diet in patients with high and very high risk.

Hypercholesterolaemia — first-line drugs include HMG-CoA reductase inhibitors (statins). The combination therapy and the intolerance to statins require the use of selective cholesterol absorption inhibitors (ezetimibe) and anion exchange resins. (Coleselam (resins) is currently unavailable in Poland.)

Inhibitors of PCSK9 may be useful in combination therapy with a maximum tolerated dose of statin and ezetimibe in patients with FH or in patients with very high cardiovascular risk, who fail to achieve treatment goals on statin with ezetimibe. PCSK9 inhibitors may be considered in cases of statin intolerance [2, 7].

Hypertriglyceridaemia — the treatment involves the use of statins, fibrates, and omega-3 polyunsaturated fatty acids (omega-3 PUFAs). Pharmacotherapy should be considered if, despite modified lifestyle, TG level exceeds 2.3 mmol/L (> 200 mg/dL) and cardiovascular risk is high. Treatment starts with a statin and if the TG level still exceeds 2.3 mmol/L, the addition of fenofibrate and then esters of omega-3 may be considered [2].

Low levels of HDL-C — an increase in HDL-C can be achieved by using fibrates and statins; however, no therapeutic goals were defined [2].

10. MONITORING THE EFFECTIVENESS OF TREATMENT AND OF SIDE EFFECTS
Initiation of pharmacotherapy should be preceded by the determination of lipid profile, CK, and ALT [2]. The determination of lipid profile should be performed at least twice within 1–12 weeks before therapy initiation, as well as after 8 ± 4 weeks of its use. Control tests should be performed at the same intervals after the change of treatment until target lipid levels are achieved. Further controls should take place every 12 months [2].

Implementation of treatment monitoring is an essential component of treatment of dyslipidaemia.

Rare side effects while taking statins include myopathy (0.5%) and increased hepatic enzymes (0.5–2%). Muscle pain without increasing CK is reported by up to 10–15% of patients [2]. These drugs may increase the risk of developing diabetes, but the benefits of using them far outweigh the risk (diabetogenic effect mostly concerns patients with fasting blood glucose > 100 mg/dL, TG > 150 mg/dL, obesity, and history of hypertension). (Experts from the American National Lipid Association suggest determination of blood glucose or glycated haemoglobin prior to use of a statin and during the first year of treatment in patients at increased risk for diabetes.)

The risk of myopathy is increased by advanced age and some drugs and diseases (Appendix 2) [8].

In the case of myalgia, and if CK is ≥ four times the upper normal limit, statin therapy should be stopped immediately, kidney function should be checked, and CK monitored every two weeks [2]. Indications for withdrawal of therapy or dose reduction of statins include intolerable muscle symptoms despite normal levels of CK. It is necessary to inform the patient about the warning symptoms such as weakness and/or muscle pain, which may occur during therapy.

Both ALT and CK should be evaluated before starting statin therapy, but there is no need to monitor them during treatment. Determination of ALT should be performed if a patient develops clinical symptoms of hepatotoxicity, such as unusual tiredness and weakness, loss of appetite, pain in the upper abdomen, dark urine, or jaundice. If ALT levels exceed three times the upper normal limit, it is recommended that statin therapy is discontinued or its dose reduced and then retesting after 4–6 weeks. This does not exclude cautious reintroduction of therapy after normalisation of enzyme activity [2].

Contraindications to statins include: pregnancy, breast-feeding, and active liver disease (acute viral hepatitis, alcoholic liver disease, decompensated cirrhosis, acute liver failure). There is no contraindication to the use of statins in the case of chronic liver disease, such as non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, chronic hepatitis B or C, and primary biliary cirrhosis.

Before using a fibrate, it is advised to assess kidney function (GFR most preferably) and determine ALT. Contraindications to the use of fibrates include: active liver disease, chronic kidney disease stage 5, gallstones, pregnancy, breast-feeding.

APPENDIX 1 [2, 3]
Non-pharmacological treatment depending on the type of dyslipidaemia:

— Hypercholesterolaemia — it is recommended to replace saturated fats, i.e. animal fats, with unsaturated fats, i.e. vegetable fats, to avoid the trans-unsaturated fatty acids (hydrogenated vegetable oils, for example, hard margarine, ready confectionery), to reduce dietary cholesterol intake, and to increase the intake of dietary fibre. The use of phytosterols and phytostanols (special margarine, www.kardiologiapolka.pl
yogurt, and nutritional supplements) can reduce LDL-C levels by 10%.

— Hypertriglyceridaemia — reduction of excess body weight, alcohol consumption (in case of severe hypertriglyceridaemia — total alcohol abstinence), consumption of, in particular, mono- and disaccharides (sugars, e.g. fructose and sucrose), and reduction of total carbohydrates and increase in physical activity and the use of preparations with omega 3 fatty acids (especially in severe hypertriglyceridaemia). Patients with severe hypertriglyceridaemia should be on a very low fat diet (fat intake limited to < 10% of total energy intake). The recommendation includes both saturated and unsaturated fats.

— Low levels of HDL-C — it is recommended that patients increase physical activity, reduce the intake of trans fatty acids and carbohydrates, normalise of body weight, and stop smoking.

**APPENDIX 2** [8]

**Factors that increase the side effects of statins**

The risk of myopathy is increased by:

— concomitant drug therapy — fibrates (primarily gemfibrozil), calcineurin inhibitors (cyclosporine and tacrolimus), macrolide antibiotics (azithromycin, clarithromycin, erythromycin), azole antifungals (itraconazole, ketoconazole), protease inhibitors, calcium antagonists (diltiazem, verapamil, mibefradil), sildenafil, acenocoumarol or warfarin, digoxin, niacin, and amiodarone (in the case of simvastatin and atorvastatin);

— other factors — female sex, age (> 80 years), low body weight, uncompensated hypothyroidism, renal and hepatic diseases, alcohol abuse, consumption of high quantities of grapefruit juice, vitamin D deficiency, high level of physical activity, genetic predisposition, history of myopathy due to previous hypolipidaemic treatment, idiopathic muscle cramps, history of increased CK, muscle symptoms in family.

**Conflict of interest:** none declared

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**References**


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