Polish Forum for Prevention Guidelines on Dyslipidaemia

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Introduction

In 2007, the European Society of Cardiology (ESC) published the next revised version of the *European guidelines on cardiovascular disease prevention in clinical practice* [1]. The authors of these recommendations advocated their implementation by national societies of cardiology and highlighted the appropriateness of their adaptation to the local conditions. It is a known fact that the 10-year risk of fatal CVD is different among various European countries with the same risk factor values, due to different lifestyles, dietary habits in particular. Therefore, it is recommended for every country to develop their own risk chart SCORE. Poland has already met this expectation. However, due to the downward trend of cardiovascular deaths (during the years 1991-2006, by approx. 40% for both sexes) [2], which results, among others, from positive changes of dietary habits of the Polish population, the SCORE chart needs periodical revisions from time to time.

Management of lipid disorders, hypercholesterolaemia in particular, constitutes a significant part of the European document, taking into account the dominating pathogenetic role of this risk factor and its vast spread among the population. This is also true for Poland [3]. Therefore, the Polish Forum for Prevention, associating representatives from eight Polish scientific societies – including the Polish Society of Cardiology as a leader – has undertaken, on behalf of those societies, an initiative to reach a consensus on dyslipidaemia management. These guidelines are to a large extent based on the ESC guidelines. The same serum lipid values have been accepted as abnormal, and the same treatment goals for LDL-C have been proposed, depending on the risk of cardiovascular death.

The treatment of hypercholesterolaemia pays special attention to the nutritional changes, with the key recommendation to reduce saturated fatty acids (SAFA) intake. Following the experts from the National Cholesterol Education Program (NCEP), we advocate a diet which includes SAFA <7% of the total energy value [4], or below 15 g per day. Patients adherence to this recommendation may be supported by food composition tables, prepared for facilitating this task [5]. Furthermore, the necessity to limit the intake of food products which include trans unsaturated fatty acids to the absolute minimum is also highlighted. In Poland, such products include mainly ready-made confectionery and bakery products. The recommended type

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of fat for food preparation is rapeseed or olive oil. It should be stressed that the spectacular decrease in cardiovascular deaths in Poland was achieved also by means of a gradual decrease in the consumption of animal fats and increase in the consumption of vegetable fats [6]. Whereas in 1989 animal fats were dominant in the diet of the Polish population, this situation has changed in the opposite direction.

The dietary treatment of hypertriglyceridaemia pays special attention to the restriction of carbohydrate intake, refined sugars in particular, and alcohol, as well as to the reduction of body mass for obese patients. If a patient suffers from the chylomicronaemia syndrome, he or she should be on a very low-fat diet and stop alcohol consumption, taking into account the high risk of acute pancreatitis.

In the case of mixed hyperlipidaemia, the patient's diet should consider dietary recommendations for both hypercholesterolaemia and hypertriglyceridaemia.

The drug of choice for patients with an increased serum LDL-C concentration is statin. The dose of statin should be designated individually for each patient in order to achieve the target level of this lipid. Taking into account the low LDL-C treatment goal in the case of secondary prevention of CVD, statin treatment is recommended for all patients. In the case of acute coronary syndrome, a high dose of statin is given regardless of the baseline LDL-C.

If the treatment goal for LDL-C is not achieved in spite of the patient's taking a tolerated dose of statin, combined lipid lowering therapy should be considered, i.e. an addition of ezetimibe or anion exchange resin.

To our mind the concentration of LDL-C should not be decreased <1.3 mmol/l. We have come to this conclusion on the basis of opinions from other experts [5] and the results of our own studies [7]. Among Polish newborns, the concentration of this lipid in umbilical cord blood is 29.8±12.8 mg/dl, and the 95th percentile is 50 mg/dl (1.3 mmol/l).

If the serum triglycerides ≥2.3 mmol/l and the LDL cholesterol is low, fibrates or slow-release nicotinic acid are applied, whereas when the serum LDL-C level exceeds the target value (mixed hyperlipidaemia), combined lipid-lowering therapy should be considered, beginning with the application of statin and followed (after 6 weeks) by a lipid profile assessment and addition of fibrate or nicotinic acid.

In severe hypertriglyceridaemia (TG ≥5.6 mmol/l), regardless of the total cholesterol concentration, fibrates or nicotinic acid are applied from the beginning and often combined with an omega-3 fatty acid preparation.

Fibrates and nicotinic acid remain as the drugs to be used in order to increase the concentration of HDL-C.

To conclude, the effectiveness of dyslipidaemia treatment, documented in numerous clinical studies, by decreasing the occurrence of cardiovascular events, justifies the necessity to continue the training of physicians in the scope of diagnosis and therapy. The guidelines are designed to support this objective.

Guidelines

1. **Dyslipidaemia's** characteristic feature 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:
   - hypercholesterolaemia – total cholesterol concentration (TC) ≥5.0 mmol/l (≥190 mg/dl) and (or) LDL cholesterol concentration (LDL-C) ≥3.0 mmol/l (≥115 mg/dl),
   - hypertriglyceridaemia – triglyceride concentration (TG) ≥1.7 mmol/l (≥150 mg/dl),
   - low HDL cholesterol concentration (HDL-C) <1 mmol/l (<40 mg/dl) in men and <1.2 mmol/l (<45 mg/dl) in women,
   - mixed hyperlipidaemia.

   Primary dyslipidaemia is most often the result of the impact of environmental factors (such as unhealthy diet, low physical activity and smoking) on an underlying genetic defect.

   Secondary dyslipidaemia may occur in the course of other diseases or be influenced by administration of drugs (see Appendix to the Guidelines).
2. **Occurrence** of increased TC concentration in the adult Polish population (WOBASZ study) is estimated in men and women at 67% and 64% respectively, of increased LDL-C concentration at 60% and 55% respectively, of hypertriglyceridaemia at 32% and 20% respectively, and low HDL cholesterol concentration at 15% and 17% respectively. Dyslipidaemia often occurs with other cardiovascular disease (CVD) risk factors and may be a component of metabolic syndrome.
3. **CVD risk** is increased in hypercholesterolaemia and in low HDL-C concentration and to a lesser extent in hypertriglyceridaemia (some species of triglyceride-rich lipoproteins are atherogenic).
4. **Screening tests** for dyslipidaemia should be carried out in every person over twenty every five years. At TC concentration <5 mmol/l (<190 mg/dl) and 10-year risk of death due to CVD <5%, according to the SCORE chart, determination of no other lipid parameters is currently indicated.

Measurement of full lipoprotein profile (TC, LDL-C, HDL-C and TG concentration) is recommended in case of: established atherosclerotic CVD, total CVD risk according to SCORE ≥5%, TC concentration ≥5 mmol/l, positive family history for early CVD, occurrence of diseases accompanied by secondary dyslipidaemias, such as diabetes, hypothyroidism and chronic kidney disease.

In adult diabetic patients, a full analysis of serum lipoproteins should be performed at the moment of disease identification; in the case of LDL-C <2.5 mmol/l (<100 mg/dl), HDL-C >1.0 mmol/l in men or >1.3 mmol/l

(<50 mg/dl) in women, TG <1.7 mmol/l without hypolipaemic therapy, control conducted every 2 years is indicated. If it is a result of its application: 2-3 times a year. In families with genetically conditioned hypercholesterolaemia, evaluation of lipoprotein profile should be carried out for the first time at the age of 2 years.

5. **A complete lipoprotein profile** should be measured in plasma or serum of venous blood taken in the fasting state, i.e. at least 9-12 hours from the last meal. In patients with acute coronary syndrome it should be obtained within 24 hours from occurrence of the symptoms. TC, HDL-C and TG concentrations should be determined using the direct method. LDL-C concentration may be calculated on the basis of Fredewald's formula or determined using the direct method (when TG ≥4.5 mmol/l i.e. 400 mg/dl). Diagnostics of chylomicronaemia syndrome (cold flotation test) should be carried out, if TG concentration ≥11 mmol/l (1000 mg/dl).
6. **In dyslipidaemia management** an evaluation and control of all CVD main risk factors should be included. Before starting the therapy, in particular the pharmacological one, secondary causes of dyslipidaemia should be excluded, since treatment of the basic disease may be sufficient. The main objective of dyslipidaemia therapy is decrease of LDL cholesterol concentration.
   - For persons without CVD symptoms, without diabetes, of total risk according to SCORE <5%, reduction of TC <5.0 mmol/l and LDL-C <3.0 mmol/l by means of non-pharmacological treatment is indicated. In case of severe hypercholesterolaemia (TC ≥8 mmol/l or LDL – C ≥6 mmol/l), immediate pharmacotherapy is highly recommended.
   - For persons without CVD symptoms, without diabetes, of total risk according to SCORE ≥5%, reduction of TC concentration <5.0 mmol/l and LDL-C concentration <3.0 mmol/l by means of non-pharmacological treatment, accompanied by control of total risk and fasting lipids after three months, is indicated. If the therapeutic goals are met, annual re-evaluation is recommended. If after three months the risk is still ≥5%, treatment as below is indicated.
   - For persons with identified CVD, diabetes type 2 or diabetes type 1 with microalbuminuria, persons with severe hypercholesterolaemia as well as persons without CVD symptoms but of total risk according to SCORE ≥5%, maintained despite 3 months long change of lifestyle, reduction of TC concentration <4.5 mmol/l (<175 mg/dl) and LDL-C concentration <2.5 mmol/l (100 mg/dl) by means of non-pharmacological and pharmacological treatment is recommended. It is beneficial to aim at further decrease in lipid concentrations: TC <4 mmol/l (<155 mg/dl) and LDL-C <2 mmol/l (<80 mg/dl). However, concentration of LDL-C <1.3 mmol/l (<50 mg/dl) should not be reduced.
   - For persons with identified ischaemic heart disease and diabetes, decrease of LDL-C concentration <1.8 mmol/l (70 mg/dl) is justified.
   - In case of no contraindications, administration of statins, without considering the initial values of serum lipids, in all patients with established CVD is indicated. In patients with acute coronary syndrome, statins should be administered before checking out.
7. **Non-pharmacological treatment**, i.e. change to diet, increase of physical activity, reduction of body mass and stopping smoking, should be advised to any patient with dyslipidaemia (see Appendix to the Guidelines).
8. **Pharmacological treatment** – monotherapy:
   - Hypercholesterolaemia – the following pharmacological agents can be applied: HMG CoA reductase inhibitors (statins), anion exchange resins, selective cholesterol absorption inhibitors (ezetimibe). Statins should be the first choice drugs. Application of anion exchange resins and nicotinic acid are often restricted by adverse effects. In addition, resins increase triglyceride concentrations in patients with hypertriglyceridaemia. Ezetimibe is of moderate hypolipaemic effect and is usually administered together with statin. In patients with severe hypercholesterolaemia (genetic disorder) carrying out of LDL apheresis may be necessary.
   - Hypertriglyceridaemia – the following drugs can be applied: fibrates, nicotinic acid, statins and omega-3 lipid acid esters. Treatment method depends on TG concentration:
     – TG: 2.3-5.6 mmol/l (200-499 mg/dl) – it is indicated to start the therapy with statins, if concentration of LDL cholesterol is higher than the target one, or with fibrates or nicotinic acid, if concentration of LDL-C is equal to the target value. The main objective is to reduce CVD risk.
     – TG: ≥5.6 mmol/l (≥500 mg/dl) – it is indicated to start the therapy with fibrates or nicotinic acid together with esters of ethyl omega-3 lipid acids to prevent acute pancreatitis first and to reduce CVD risk. A ban on alcohol consumption and a low-fat diet are obligatory (if a plasma sample refrigerated overnight shows a creamy supernatant); furthermore, improvement of glycaemia control in diabetics and withdrawal from oestrogen therapy are vital.
     – TG: 1.7-2.3 mmol/l (150-199 mg/dl) is not a direct objective of pharmacotherapy. Achievement of target values of LDL-C by means of statins in order to reduce CVD risk is considered a priority.
9. **Combined lipid-lowering treatment:**
   - severe hypercholesterolaemia – if statin treatment fails to achieve the target LDL-C concentration, it is recommended to add ezetimibe (additional decrease of LDL-C concentration by 18-20% is possible) or anion exchange resin;
   - mixed hyperlipidaemia (increased LDL-C and TG) – after initial therapy with statins, we may add fibrate or nicotinic acid, and esters of omega-3 fatty acids as the third-choice drug;

- chylomicronaemia syndrome – combination of fibrate with esters of omega-3 fatty acids (in the amount of 2-4 g/day) is recommended.

10. Monitoring of effectiveness and adverse effects constitutes an indispensable element of hypolipaemic treatment.

It is recommended to control lipoprotein profile and, if necessary, change to therapy every 6 weeks, until the moment of achieving the target lipid concentration. Further controls should be conducted every 4-6 months.

Rare side-effects in the course of statin administration are as follows: myopathy (0.5% of patients) and increase in liver enzymes activity (2% of patients).

Myopathy risk is increased by advanced age and some drugs and diseases (see Appendix to the Guidelines). Routine creatinine kinase (CPK) control in patients treated with statins is not recommended, but it is necessary to inform the patient of any warning symptoms in the form of weakness and/or muscle pains. An indication for immediate withdrawal of treatment is acute muscle pain and increase of CPK concentration >10 times the upper limits of normal.

Aspartate and alanine transaminases (AST and ALT) should be evaluated before starting the therapy, and then after 6 and 12 weeks and in the long-term period 2-3 times a year (usually simultaneously with lipid profile control). If transaminase concentrations exceed the upper limits of normal value by more than 3 times, it is indicated to withdraw statins and conduct detailed hepatological diagnostics. The above does not exclude attempts to apply another statin to therapy after normalization of enzyme activity.

Contraindications to administration of statins are pregnancy, breastfeeding and active liver disease.

Before administering fibrates it is recommended to assess kidney function (GFR as the most recommended) and measure the ALT and AST activity. Contraindications to administration of fibrates are: active liver disease, chronic kidney disease in the fifth stage, cholelithiasis, pregnancy and breastfeeding.

Appendix

Point 1. Causes of secondary dyslipidaemia.

Secondary dyslipidaemia may occur in hypothyroidism, obstructive jaundice, primary biliary cirrhosis, chronic kidney disease, alcoholism, diabetes, obesity, multiple myeloma, anorexia nervosa, bulimia, lipodystrophy and when using thiazide diuretics, corticosteroids, cyclosporine, oestrogens, progestagens, retinoids and protease inhibitors.

Point 7. Non-pharmacological treatment of dyslipidaemia.

- **Dietary modification** (See *Kardiologia Polska* [8]):
  - reduction of LDL-C concentration should be achieved by lower consumption of saturated fatty acids and trans-isomers of unsaturated fatty acids, their replacement with unsaturated fatty acids, reduction of cholesterol consumption, and consumption of products enriched with plant sterols or stanols,
  - reduction of TG concentration should be achieved by decrease in consumption of carbohydrates, particularly refined sugars, and alcohol,
  - in chylomicronaemia syndrome a diet of low fat content is applied, i.e. less than 20 g a day (less than 10% of daily caloric requirement).

It should be remembered that a diet aiming at atherosclerosis prevention must be enriched with anti-oxidants, which is ensured by high consumption of fruits and vegetables.

- **Increase in physical activity** – reduces TG concentration, increases HDL-C concentration.
- **Body mass reduction** – reduces LDL-C and TG concentration, increases HDL-C concentration.
- **Stopping smoking** – increases HDL-C concentration.

Point 10. Drugs and diseases increasing myopathy risk in persons taking statins.

Myopathy risk is increased by fibrates (mainly gemfibrozil), calcineurin inhibitors (cyclosporine and tacrolimus), macrolide antibiotics (azithromycin, clarithromycin, erythromycin), azole anti-fungal drugs (itrakonazol, ketokonazol), protease inhibitors, calcium antagonists (diltiazem, verapamil, mibefradil), sildenafil, warfarin or acenocoumarol, digoxin, niacin, and amiodarone (in case of simvastatin and atorvastatin). It is also increased in emaciated persons or persons suffering from hypothyroidism and kidney failure.

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