**NATIONAL ASSOCIATION OF
GENERAL PRACTITIONERS IN BULGARIA**

BULGARIAN SCIENTIFIC SOCIETY OF GENERAL MEDICINE

GUIDELINES
FOR THE MANAGEMENT OF LIPID DISORDERS (DYSLIPIDAEMIA) FOR GENERAL PRACTITIONERS

Guidelines Development Committee

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**NATIONAL ASSOCIATION OF
GENERAL PRACTITIONERS IN BULGARIA**

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The present guidelines have been developed based on the information from adopted and approved by numerous world, European and Bulgarian scientific societies recent clinical studies and aims at supporting general practitioners in their practical work. The referent sources are listed in Annex No. 12.

The present Guidelines have been discussed on 13 consensus meetings on dyslipidaemia in 2006 with the participation of general practitioners from all regions of Bulgaria.

USED ABBREVIATIONS:

FFA *– Free Fatty Acids*

TC *– Total Cholesterol*

CE *– Cholesterol Esters*

TG *- Triglycerides*

PHL *- Phospholipids*

DLP *- Dyslipidaemia*

HDL *– High Density Lipoproteins*

LDL *– Low Density Lipoproteins*

VLDL – *Very Low Density Lipoproteins*

IDL *– Intermediate Density Lipoproteins*

CK *- Creatine Kinase*

IHD *– Ischaemic Heart Disease*

CVD *– Cerebrovascular Disease*

PVD *– Peripheral Vascular Disease*

ABP *– Arterial Blood Pressure*

G.P.- *General Practitioner*

Over the last 15 years the morbidity and mortality caused by atherosclerotic vascular disease in our country has risen. The reasons vary, however, of particular importance is the wide distribution of a number of risk factors, e.g. poor diet, obesity, reduced physical activity, alcohol overuse, smoking etc., along with certain diseases, such as diabetes mellitus, arterial hypertension etc.

A number of trials have established that lipid disorders (dyslipidaemia) are of utmost importance in the pathogenetics of atherosclerosis. The presence of dyslipidaemia in combination with some other risk factors can lead to damage of the medium and big artery walls, which promotes atherosclerosis in the three main vascular areas – the brain, the heart and the limbs. As a result, organ disorders take place, which clinically present as ischaemic heart disease (IHD), cerebrovascular disease (CVD) and peripheral vascular disease (PVD).

The general practitioner, being in continuous relationship with their patients, has the greatest opportunity for early detection, prevention and treatment of dyslipidaemia. Should their efforts prove successful, not only can the risk of early atherosclerosis be reduced among the Bulgarian population, but also the morbidity caused by atherosclerotic vascular disease.

These guidelines aim at the general practitioners, trying to assist them in their activities towards treating patients with dyslipidaemia.

I. LIPIDS AND LIPOPROTEINS

"Lipids" is the term used to denote a group of certain soluble in organic solvents and insoluble in water substances. Lipids in human body are presented by several types: **free fatty acids** (FFA), **total cholesterol** (TC) and **cholesterol esters** (CE), **triglycerides** (TG) and **phospholipids** (PHL).

Free fatty acids are part of the structure of TG, PHL and CE and affect their properties.

Triglycerides (triacylglycerols) constitute esters of glycerol with free fatty acids, and are the main lipid component in the body. They enter the body predominantly with food and are a major energy source.

Cholesterol is a representative of the sterol group and is found in free and ester form only in animal tissues. It is an important element of all cell membranes and participates in the biocynthesis of biliary acids, adrenocorticotrope hormone, androgenes, oestrogenes and progesterone, and is a vitamin D precursor. The TC amount depends on its production within the body (80% is synthesized in the liver), and its contents in the food (around 20%).

Phospholipids are esters of glycerol with fatty acid remnants and phosphoric acid. In the body they are synthesized in the liver and intestinal mucosa. Their main function is to support the structural integrity of cells.

The fats absorbed in the gastrointestinal tract and synthesized in the body are transported to the places where they are either stored or metabolized through transport lipids.

The blood transport is organized through aggregates of lipid molecules (TC, CE, TG and PHL) and specific proteins (apoproteins) called **lipoproteins**. They play important role in lipid metabolism.

The main lipoproteins are: chilomicrons, high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). The atherogenic capacity of lipoprotein molecules are defined by their size, density, percent ratio between the protein and lipid part, and their blood concentration **(*Annex 1*).**

Lipids and lipoproteins, literally, have no referent ranges, i.e. "from – to", as typical for other biochemical substances (indexes). Their referent ranges depend on the patient risk

category and the total cardiovascular risk evaluation. Therefore, they serve for determining the doctor's approach in the process of prevention and treatment.

In practice, most frequently target levels of total cholesterol and lipoproteins are used, as set out in the third report of the American National Cholesterol Education Program (*NCEP, Adult Treatment Panel III, 2001*) and Update 2004. **(*Table 1a and 1б)***

Table 1a. Target Levels of Lipids and Lipoproteins for Treatment Purposes (in mmol/l)
NCEP, Adult Treatment Panel III, 2001

LDL-C	Level	TC	Level
Ideal	< 2.6	*Desirable*	< 5.2
Almost ideal	2.6 - 3.3	*Borderline*	5.3 - 6.1
Borderline	3.4 - 4.1	*High*	> 6.2
High	4.2 - 4.8	**TG**	
Very high	> 4.9	*Normal*	< 1.7
HDL-C mmol/L		*Borderline*	1.7 - 2.18
Low	< 1.0	*High*	2.3 - 5.4
High	> 1.6	*Very high*	> 5.5

Table 1б. Target Levels of Lipids and Lipoproteins for Treatment Purposes (in mmol/l)
Adult Treatment Panel III Update, 2004

Asymptomatic Subjects	TC < 5.0	LDL-C < 3.0
Subjects with CVD Symptoms	TC < 4.5	LDL-C <2.5
Subjects with Diabetes Mellitus	TC < 4.5	LDL-C <2.5
Markers of Increased Cardiovascular Risk	HDL-C < 1.0 males HDL-C < 1.2 females	TG > 1.7

The target levels concern the three risk categories of patients, defined in accordance with the recommendations of the International and European Atherosclerosis Association. **(*Table 2)***

Table 2. Target Levels of LDL-C and non -HDL-C, according to the patient's risk category

RISK CATEGORIES	10 YEAR RISK	LDL-C TARGET (mmol/l)	NON-HDL-C TARGET (mmol/l)
0 - 1 risk factor	10 year risk ≤ 5%	< 4.1 mmol/l	< 3.4 mmol/l
> 2 risk factors	10 year risk ≤ 20%	< 3.4 mmol/l	< 4.1 mmol/l
IHD or equivalent of IHD risk	10 year risk > 20%	< 2.6 mmol/l	< 4.9 mmol/l

Achieving the target levels in patients from different risk categories by lipid lowering drugs and methods is an important objective for the general practitioner, whose appropriate decision can prevent occurrence or stop development of atherosclerosis, thence prevent from premature death or improve the quality of life of patients with cardiovascular diseases.

II. LIPID DISORDERS (DYSLIPIDAEMIA)

The term „lipid disorders" or dyslipidaemia (DLP) stands for the disturbed ratio and levels in the different lipid groups and lipoproteins in human blood. In its essence, dyslipidaemia is a disease of the lipid and lipoprotein metabolism. It has a complex etiopathogenetic mechanism, which determines increased production of lipids or slowing-down and disturbing lipid catabolism. The impaired lipid metabolism, along with other risk factors, leads to gradual damage of the big and medium artery walls and development of atherosclerotic process.

The different mechanisms of development and types of disorders determine the variety of dyslipidaemias, which creates serious difficulties in their classification. 3 classification principles are used in clinical practice: etiopathogenetic, biochemical and therapeutic one.

According to the etiopathogenetic principal dyslipidaemia is divided into **primary** and **secondary** one**.**

Primary dyslipidaemia develops independently and is not related to other disorders in human body. Depending on its etiology it can be **genetic** and **non-genetic**.

Primary genetic dyslipidaemia is a result of a genetic defect and is hereditary.

Primary non-genetic dyslipidaemia is caused by different in their type and character external factors, e.g. poor diet, physical inactivity, smoking etc. (***Annex 11***)

Secondary dyslipidaemia is a consequence of certain biliaryhepatic, renal, metabolic, hormonal, infectious and neoplastic diseases. (***Annex 11***)

According to the biochemical classification (**by Fredrickson**) dyslipidaemia is divided into 6 phenotypes:

- Type I – **family hyperchilomicronaemia** in children (slightly increased cholesterol level and high triglyceride level)
- Type II A – **family hypercholesterolaemia** (increased cholesterol level and normal triglyceride level)
- Type II B – **family combined hyperlipidaemia** (increased cholesterol and triglycerides level)
- Type III – **family dysbetalipoproteinaemia** (increased cholesterol and triglycerides level)
- Type IV – **primary hypertriglyceridaemia** (high triglyceride level and normal cholesterol level)
- Тип V – **family hyperchilomicronaemia** in adults (high triglyceride level and normal or slightly increased cholesterol level)

In common use, convenient is the therapeutic classification of the three types of dyslipidaemia adopted by the European Atherosclerosis Society (**EAS**):

1. **Hypercholesterolaemia** (raised total cholesterol and LDL-C levels)
2. **Combined** (mixed) **hyperlipidaemia** (raised levels of total cholesterol, triglycerides, LDL-C and VLDL-C)
3. **Hypertriglyceridaemia** (increased VLDL-C and TG levels)

Dyslipidaemia as a metabolic disorder has asymptomatic course before atherosclerosis has occurred.

The development of organ atherosclerotic changes in the respective vascular area should imply to the general practitioner to seek for dyslipidaemia.

The diagnosis of dyslipidaemia is a laboratory one, where the lipid profile indexes are tested (amount of separate lipid components).

To obtain reliable results from the laboratory lipid profile analysis certain requirements during the test should be met:

- Fasting 12-14 hours before the laboratory tests;
- Abstaining from alcohol for 48 hours, and abstaining from smoking and coffee on the day of analysis;
- Women not in menstrual cycle;
- No bacterial or viral infections present.

Blood tests for TC and HDL-C can be done at any time over the clock, whereas TG and LDL-C should be tested obligatory after fasting.

The familial character of laboratory diagnosed dyslipidaemia should be accepted only at the condition that it has been detected in not fewer than 2 blood relatives.

The early detection of dyslipidaemia, before the organ disorders and respective clinical symptoms have taken place, is possible only through medical screening.

3 strategies are used in the screening of dyslipidaemia:

- **General-Population** – the whole adult population is screened;
- **Group-Risk –** the subjects at risk are screened;
- **Opportunistic** – the subjects visiting the general practitioner for other reasons are screened.

The ***Group-Risk Strategy*** is applied predominantly in the general medical practice, which covers subjects who, due to the presence of risk factors, are likely to develop atherosclerosis.

The main screening test for DLP comprises measurement of TC level in blood samples obtained from venepuncture or finger prick.

If average levels of TC < 5.0 mmol/l (from 2 tests within 1 - 8 weeks) are detected, the next screening test should take place in 5 years.

Values of TC > 5.0 mmol/l require examination of lipid status (TC, TG, HDL-C, LDL-C and VLDL-C).

The dyslipidaemia selective screening is recommended once a year for the following categories of patients:

- Adults and children with familial history of early coronary heart disease, cerebrovascular disease and diabetes mellitus;
- Men aged 35 – 55 years;
- Women aged 45 – 65 years;
- Subjects at multiple risk factors, or one strong risk factor.

III. DYSLIPIDAEMIA AND ATHEROSCLEROSIS

Atherosclerosis is a disease of the medium and big arteries which develops under the influence of numerous genetic, behavioural and other factors of environment. It affects mainly the arteries of the 3 large vascular areas and is clinically manifested as **coronary (ischaemic) heart disease, cerebrovascular and peripheral vascular disease**.

The lipid/ lipoprotein role as a factor for the atherosclerosis development has been confirmed not only clinically, but also experimentally. The lipid hypothesis identifies atherosclerosis as a result of impaired endothelium function and chronic inflammation of arterial walls as lipids build up in the intimate layer of the arteries, which is followed by fibrosclerosis, depositing of calcium, and eventually – narrowing of the arterial lumen.

The main pathogenetic factor is increased level of cholesterol carried by LDL-C.

The intact endothelium of big blood vessels limits penetration of lipoproteins. Number of factors could impair its integrity and condition enhanced permeability (e.g. increased arterial pressure, increased turbulence in the zone of vascular bifurcation, metabolic impacts, raised levels of catecholamine, serotonin, angiotensin etc.).

A typical pathomorphologic substrate of atherosclerosis is the atherosclerotic plaque in the intimate layer of the arterial vessel. It occurs gradually, as monocytes which cross endothelium due to increased permeability transform into macrophages and "foam cells". So activated macrophages capture and swallow oxygenated LDL-C. As lipid accumulation progresses, first intracellularly, then extracellularly, fatty spots start to form. As the fatty spots grow, they form a "lipid core" with consequent formation of a fibrose hat containing collagen, proteoglycanes and activated smooth muscular cells, whereupon an atherosclerotic plaque is formed. ***(Annex 2)***

In the process of atherosclerotic plaque development under the influence of number of various factors the plaque tends to rupture, followed by development of thromboses or haemorrhages, and total or partial occlusion of the arterial vessel (unstable plaque). The clinically unstable plaque is manifested as a severe vascular event (coronary, cerebral or peripheral vascular one).

The smallest lipoproteins - HDL – easily penetrate the vessel wall, however, they "leave" it easily, and do not, therefore, cause atherosclerosis.

LDL, IDL and VLDL penetrate endothelium and reach the intimate layer of the vessel wall, where they start oxidative stress, decrease nitrous oxide concentration and initiate development of atherosclerotic changes.

A strong positive link has been established between LDL-C and the risk of atherogenic vascular diseases in men and women, regardless of their age.

An increase of cholesterol by 10% leads to an increase of morbidity of IHD by 27%, whereas its decrease by 25% leads to a decrease of morbidity by 25%.

The epidemiologic studies associated with angiographic and final clinical evaluations confirm the **importance of LDL as a main factor for the development of atherosclerosis.**

The atherogenic LDL-C related risk increases with the presence of other risk factors, e.g. low HDL-C, smoking, arterial hypertension, diabetes mellitus etc.

Decreasing LDL-C is the main objective for the general practitioner in cases of detected dyslipidaemia, regardless of whether the dyslipidaemia is asymptomatic or organ disorders have already taken place.

Hyperlipidaemia leads to a risk of atherosclerotic disease too, however, the link is not as strong as in hypercholesterolaemia. A value of TG > 1.7 mmol/l is a marker for an increased risk. Low levels of HDL-C condition early development of atherosclerosis and are a poor prognostic marker in subjects with already clinically manifested cardiovascular disease. They are formed

under the influence of certain risk factors, among which of utmost importance are smoking, low physical activity, diet high in white sugar and carbohydrates, animal products etc.

Levels of HDL-C under 1.0 mmol/l in men and under 1.2 mmol/l in women are regarded as a marker for increased risk and suggest the additional concomitant risk factors be obviated.

High TG and low HDL-C levels increase the atherogenic risk. This combination is typical for subjects with diabetes mellitus type II with abdominal obesity, insulin resistance and low physical activity, and demands compulsory administration of lipid-lowering drugs. Dyslipidaemia and especially hypercholesterolaemia occupy a main place in the atherosclerosis related factor constellation, as shown in the qualification scheme below:

MAIN GROUPS AND TYPES OF ATHEROGENIC RISK FACTORS:

1. **Controllable risk factors decreasing atherosclerosis rate, if managed:**

A. Behavioural

1. Smoking
2. Alcohol overuse
3. Physical inactivity
4. Psycho-emotional stress

Б. Diseases and conditions

5. Diabetes mellitus
6. Arterial hypertension
7. Left ventricular hypertrophy
8. Obesity
9. Menopause women
10. Raised LDL-cholesterol
11. Modified haemostatic factors:
    - *Enhanced thrombocyte aggregation*
    - *Raised fibrinogen levels*
    - *Raised levels of tissue fibrinogen activator and plasminogen activator inhibitor.*

2. **Uncontrollable Risk Factors:**
    1. Age
    2. Gender and race
    3. Height
    4. Heredity

Determining atherogenic risk factors in each subject, regardless of whether subjects have asymptomatic or symptomatic form of atherosclerosis, provides the general practitioner with an opportunity to define cardiovascular risk, hence an appropriate approach.

Modern strategies for prevention of atherosclerosis and treatment of atherosclerosis-related CVD are obligatory based on the cardiovascular risk evaluation.

Cardiovascular risk evaluation in each subject is a base for the general practitioner to identify the type and intensity of prevention measures, i.e. dietary regimen, life style, medication etc.

In common practice the **SCORE** system (*Systematic Coronary Risk Evaluation*) is used to measure and evaluate cardiovascular risk ***(Annex 3).***

When dyslipidaemia is present, in their prevention and treatment activities doctors should aim at reaching the so called **target levels** of TC and LDL-C, which differ, depending on the risk category which the respective patient falls in. (***Table 2***)

It is perceived that patients with a detected cardiovascular disease are at high general risk of future vascular events, which requires the most intensive interference possible in their lifestyle, diet and administered medication.

In asymptomatic individuals the total cardiovascular risk is high, with significantly strong single risk factors, such as:

- TC > 8 mmol/l (309 mg/dl)
- LDL-C > 6 mmol/l (240 mg/dl)
- Arterial Blood Pressure > 180/110 mmHg
- Diabetes Mellitus type II or type I with microalbuminuria.

These factors should be managed with maximum caution and no further risk evaluation is needed before the general practitioner decides on a preventive plan.

In healthy individuals with asymptomatic dyslipidaemia the preventive measures should be taken depending on the total risk of CVD.

After the total risk evaluation, depending on the TC and LDL-C levels, the measures listed in ***Annex 4*** should be taken.

IV. LIPID-LOWERING METHODS AND DYSLIPIDAEMIA CORRECTION METHODS

The methods and approaches used towards correction of dyslipidaemia in clinical practice are divided into two groups:

(1) Non-pharmacologic (Non-Drug);

(2) Pharmacologic (Drugs).

They are applied for primary and secondary prevention (treatment), separately or jointly, depending on the type of dyslipidaemia and rate of cardiovascular risk.

The primary prevention is indicated for subjects with dyslipidaemia, with view to preventing atherosclerosis development and its clinical complications.

The secondary prevention (treatment) is indicated for patients with clinically manifested atherosclerosis and different types of dyslipidaemia, aiming at reducing its complications.

NON-PHARMACOLOGIC METHODS AND APPROACHES

- **Life style modification** in persons with dyslipidaemia is the first step to take in the process of dyslipidaemia correction, which includes obviating the risk factors.

The general practitioner must recommend subjects with dyslipidaemia (irrespective of whether primary or secondary prevention is concerned):

- **Smoking cessation;**
- **Increase physical activity;**
- **Reduce body weight, BMI (Body Mass Index) being below 25 kg/m^2;**
- **Quit alcohol use (up to 250 ml red wine daily is permitted, moreover, it has a proved cholesterol-lowering effect);**
- **Avoid psychoemotional stress.**

Scientific studies have shown that lipid plasma levels depend on the amount of fat, carbohydrates and cholesterol in the food intake. To that end, a **lipid-lowering diet would affect significantly the primary and secondary prevention (treatment) of dyslipidaemia.**

The diet in patients with dyslipidaemia should include food where cholesterol-raising components are reduced, while the cholesterol-lowering ones are increased in their amount. It is known that every 100 mg cholesterol taken with food raises the serum level by 0.259 mmol/l (e.g. 1 yolk contains approximately 250 mg cholesterol and raises the total cholesterol by approximately 0.65 mmol/l).

Cholesterol-raising factors in food, i.e. saturated fatty acids, foods high in cholesterol and coffee should be excluded, or significantly reduced.

Cholesterol-lowering factors in food, i.e. unsaturated fatty acids (mono- and polyunsaturated), garlic, vitamins E and C, betacarotin etc. lead to a decrease of total cholesterol and LDL-C levels and an increase of HDL-C level.

When diet for subjects with dyslipidaemia is planned the general practitioner must abide by the recommendations of the European Atherosclerosis Society (**EAS**):

1. **Reducing total fat intake;**
2. **Sharp reduction of food containing saturated fatty acids and cholesterol (animal fat, cow milk, yolk, milk cream, brain, kidneys, and their nutritive derivates etc.);**
3. **Predominance of food containing polyunsaturated fatty acids (liquid vegetable oils, fish oil, fish, poultry, grains - nuts, almonds, soy-bean and peanut);**
4. **Predominance of food containing soluble polysaharides (whole grain bread, oats, soy-bean, garlic, pectin etc.);**
5. **Reduced intake of table salt up to 5 g per 24 hours.**

The doctor should recommend a certain diet by obeying the above principles and accordingly inform the patients about the approximate content of cholesterol in the separate mass use products. ***(Annex 5 and Annex 6)***

4. 2. PHARMACOLOGIC LIPID-LOWERING METHODS

Over the last years several groups of drugs have been introduced to clinical practice with different mechanisms of action, cost-effectiveness and therapeutic effect.

- **STATINS**

Statins are medicaments of first choice in the treatment of increased LDL-C, however, less effective in lowering TG. They produce benefits by reducing cholesterol irrespective of its initial concentration but patients with TC of 5 mmol/l or greater are likely to benefit most. Therefore, this group of agents should be considered for all patients at high risk of cardiovascular diseases (IHD, PVD, CVD) and diabetes mellitus, since they reduce cardiovascular events and general mortality.

Mechanisms of action: Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA) predominantly in the liver, thus blocking the cholesterol synthesis; they also increase the number of LDL-receptors in hepatocytes, which leads to enhanced uptake and catabolism of LDL-particles, and eventually increase removal of LDL.

Medical effects: Statins reduce LDL by 18% - 55%, but more pronounced reduction is observed with their initial intake, while doubling the dosage is usually followed by additional reduction of 7%. The maximum effect occurs in 4 - 6 weeks or upon change of dosage. The optimal time to take the statins is at night. (***Table 3***)

Table 3. Maximum Doses and Effectiveness of the Main Types Statins

Characteristics	Atorvastatin	Rosuvastatin	Simvastatin	Pravastatin	Lovastatin	Fluvastatin XL
Maximum Dose (mg/d)	80	40	80	40	80	80
Maximum Reduction of Serum LDL-C (%)	60	55	47	34	40	38
Reduction of Serum TG (%)	29	26	18	24	16	31
Increase of HDL-C (%)	6	9.2	12	12	8.6	12

Statins have the so called pleiotrope effects on the arterial wall – antiinflammatory and stabilizing the state of atherosclerotic plaque. ***With*** increasing the dose their efficacy towards reducing the LDL-C increases. (***Table 4***)

Table 4. Dose-Dependent Efficacy of Statins towards Decreasing LDL-C

Daily Dose (mg)	Atorvastatin	Rosuvastatin	Simvastatin	Pravastatin	Lovastatin	Fluvastatin
10	- 37%	-46%	- 30%	- 22%	-	-
20	- 43%	-52%	- 38%	- 32%	- 27%	-22%
40	- 50%	-55%	- 41%	- 34%	- 34%	- 35%
80	- 60%	-	- 47%	-	- 42%	- 38%

Side effects: headache, muscle pains, liver function disturbances, paraesthesia, gastrointestinal upset, rarely rash and hypersensitiveness, which occur and increase their intensity as the dose increases.

A risk group for development of miopathy and rabdomiolisis are patients with untreated hypothyreoidism, reduced muscle mass, renal insufficiency, women and elderly. Administration of statins should be discontinued upon 3-fold increased ALAT and 10-fold increased creatine kinase (CK), miopathy or predisposition to renal insufficiency.

The administration of statins metabolized by cytochrome P450 oxydase (Atorvastatin, Lovastatin and Simvastatin) should be avoided concurrently with Amiodarone, macrolides, Diltiazem, Verapamil, anti-viral agents and system azole antimicotics because of drug interaction. Pravastatin and Fluvastatin are exemption from this trend.

When statins are administered the dose need be reduced only in patients with severe renal insufficiency (creatinine clearance < 10 ml/min). Some statins can be administered in children, if necessary.

Administration: In common practice first choice agents are Atorvastatin and Simvastatin. They are appropriate for most patients, and at a low to average dose they reduce LDL- C by up to 30% - 40%. The rest of statins - Pravastatin, Fluvastatin etc. are recommended in case of intolerance to the first group.

According to their lipid-lowering effect the statins are put in the following order: Atorvastatin, Rosuvastatin, Simvastatin, Pravastatin, Lovastatin and Fluvastatin XL. (***Table 4***)

During statin medication the liver function must be monitored (ASAT, ALAT, ALP and GGTP). It is advisable that those values are monitored simultaneously with check of the lipid profile during the first 12 weeks.

In each patient the dose of chosen statin should be based on the level of hyperlipidaemia, co-existing drug administration and co-morbid condition until the target lipid levels are achieved.

Medication and Recommended Daily Dose (*Annex 7*)

- **FIBRATES**

Fibrates are indicated for the treatment of hypertriglyceridaemia in patients with cardiovascular disease, low HDL-C or increased triglycerides.

Mechanism of action and curative effects: Fibrates are antagonists of the activated nuclear receptors of peroxisome proliferation (PPAR) and are the most powerful, known up to now, pharmacological agents for the treatment of hypertriglyceridaemia. These agents are effective for increasing HDL-C, however, they have a different effect on LDL-C.

Gemfibrozil and Fenofibrate are the most frequently administered with similar effects: they reduce triglycerides by 40% - 50% and increase HDL-cholesterol by 10-15%.

Their effect on cholesterol depends on the initial triglyceride level: if TG are high HDL-C increases, if TG are normal HDL-C does not increase either.

Fenofibrate has an additional LDL-C-lowering effect and is a better choice in raised LDL-C and TG, and low HDL-C.

Recent studies do not evidence any significant effect when same agents are administered as monotherapy towards reducing myocardial infarction rate, therefore, they should be administered in combination with other lipid-lowering agents.

Side effects: The fibrates are well tolerated, rarely do they cause gastro-intestinal discomfort. However, they can lead to a miosite syndrome, especially in patients with impaired renal function. Further, they increase the risk of cholelithiasis and miopathy (in combination with statins) and their administration requires enzyme monitoring.

The fibrate-statin combination increases the likelihood of side effects, therefore the patient's condition should be cautiously monitored for any symptoms of muscle toxicity (pains). (***Annex 8***)

Interaction: In cases of combination Gemfibrozil-statins it has been observed that both agents interact at the stage of glucoronization, which leads to a dangerous raise in their blood levels, hence increased risk of rabdomiolisis. When a fibrate should be combined with a statin, Fenofibrate is recommended.

Medication and Recommended Daily Doses (*Annex 7)*

- **POLYUNSATURATED FREE FATTY ACIDS (omega-3-free fatty acids)**

Polyunsaturated free fatty acids (omega-3-free fatty acids) are used in the treatment of hypertrigliceridaemia; in the prevention of coronary heart disease and the reduction of cardiovascular death risk; they play significant role in the secondary prevention following acute myocardial infarction (AMI).

Mechanisms of action and curative effects: Polyunsaturated free fatty acids - eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce the TG synthesis. They are taken with food, mainly with fish and fish oil. Rich in omega-3-fatty acids are salmon, trout, tone, herring, sardine, bonito and cod-fish.

Omega-3-fatty acids have various beneficial effects, such as endothelium-protective, anti-atherogenic, anti-arrhythmogenic and anti-thrombogenic. They decrease triglyceride and cholesterol levels; take part in the prostaglandine synthesis and exert anti-inflammatory effect. At high doses PNFA decrease TG by approximately 30% - 50% and retard atherogenesis through decreasing the amount of soluble intracellular adhesion molecules and soluble E-selectine, especially in patients with diabetes mellitus.

Side effects: Unpleasant fish taste in mouth and dyspepsia (only in liquid forms), which can be improved if the drug is frozen before use. A short-term increase of blood glucose can be observed in diabetic patients; reduction of fibrinogen, reduction of thrombocyte aggregation and prolonged bleeding time; fall in blood pressure has also been observed and protective effect against ventricular arrhythmia.

At maximum dose of fish oil LDL-C can rise parallel with a decrease of TG.

Interaction: Omega-fatty acids at high doses can interact with some drugs, such as:

- ✓ Aspirin and Warfarin – omega-fatty acids prolong bleeding time in treatment with thrombocyte inhibitors or anticoagulants;
- ✓ Cyclosporine – toxic effects decrease (raised arterial blood pressure and impaired renal function) in transplanted patients;
- ✓ Local corticosteroids – psoriasis symptoms are improved;
- ✓ Statins – more effective antilipidaemic effect;
- ✓ NSAID – decreased risk of ventricular ulcer in animal models.

Medication and Recommended Daily Dose (*Annex 7*)

- **BILE BINDING RESINS (Bile Acid Sequestrants and Ion-Exchange Resins)**

The bile binding resins (bile acid sequestrants) are indicated for patients with primary and secondary hypercholesterolaemia.

Mechanism of action and curative effects: Resins partially remove bile acids from the portal circulation, hinder their re-absorption in the liver and form complexes in the intestines which are excreted. LDL-C is compensatory degraded and its clearance enhanced. These drugs reduce LDL-C efficiently but aggravation of hypertriglyceridaemia is possible.

Side effects and interaction: These lipid-lowering drugs are the less prescribed due to the plenty of side effects - sickness, vomiting, constipation, abdominal swelling and low general tolerance. However, they are comparatively safe, therefore are indicated for children and during pregnancy. In addition, they interact with certain drugs by inhibiting their absorption, therefore other oral drugs should be taken ½ -1 hour before a meal or 2 hours after taking the lipid-lowering agent. The resins can raise TG, if the TG initial levels are higher than 3.9 mmol/l.

Medication and Recommended Daily Dose (*Annex 7*)

- **NICOTINIC ACID AND DERIVATES**

Nicotinic acid and its derivates are effective in treating combined dyslipidaemia, as they can be combined with statins, if alone fail to manage the dyslipidaemia. These drugs are indicated in case of intolerance to statins and are an ideal choice in subjects with isolated raised HDL-C level.

Mechanism of action and curative effects: These drugs constitute the most powerful lipid modulator towards raising HDL-C through blocking the free fatty acid release and inhibiting the liver synthesis of VLDL (up to 15% - 35%); they further lower to a significant extent TG and averagely reduce LDL-C.

Side effects and interaction: Nicotinic acid and its derivates have limited use due to their side effects. Their major disadvantage is vasodilation, and is manifested with flushing sensation, itching and gastrointestinal upset. In the retarded release drug form (Niaspan) vasodilation is relatively slight and flush is not that pronounced. Because of its mild hyperglicaemic effect nicotinic acid can be used in patients with diabetic mellitus type II, provided the minimum raise of blood glucose is controlled through manipulation of the anidabetic therapy.

Patients requiring more caution are: *diabetics,* with view to the possibility of increasing the glucose tolerance, therefore, the glucose control should be improved; *patients at risk of podagra or urate nephropathy* considering the increase of uric acid; and *patients with ulcer disease* with regards to aggravating their symptoms.

Nicotinic acid can be administered separately, or in combination with other agents. In combination with statins it should be started at a lower dose in order to reduce the risk of hepatic toxicity, miopathy and rabdomiolisis. Monitoring the liver function and creatine kinase levels are obligatory.

Medication and Recommended Daily Dose (*Annex 7*)

- **CHOLESTEROL ABSORPTION INHIBITOR (Ezetimib)**

The cholesterol absorption inhibitor (Ezetimib) is used in hypercholesterolaemia and as an accompanying medication along with lifestyle modification, provided diet and statin administration, when the patient's response to the separately administered approaches is inadequate.

Mechanism of action and curative effects: 2-azetidinone is a new class active substance which diminishes the TC and TG intestinal absorption through selective inhibition. It decreases cholesterol in the liver and enhances its clearance from blood circulation. Ezetimib is administered as monotherapy or in combination with a diet and physical exercise to reach reduction of TC and LDL-C by up to 10% - 20%. Well tolerated, it is indicated for patients who cannot achieve the target LDL- C with statin monotherapy. The drug is active in combination with statins since it has an additive to the statin action effect, hence additional lowering of LDL-C. If statins are not well tolerated, Ezetimib can be used as monotherapy in patients with homozygote familial hypercholesterolaemia and homozygote familial sitosterloaemia. Ezetimib's absorption is decreased in combination with bile acid sequestrants.

Side effects: An insignificant raise in the liver enzymes is possible; rarely are stomach pains and muscle fatigue observed; angioedema is reported in 1 per 5,000 subjects.

Medication and Recommended Daily Dose (*Annex 7*)

When lipid-lowering agents are administered, the general practitioner can use the data presented in ***Table 5***, as well as the general recommendations for the management of dyslipidaemia in certain groups of patients, as listed in ***Annex 9 and Annex 10***.

Table 5. **Characteristics of Lipid-Lowering Drugs**

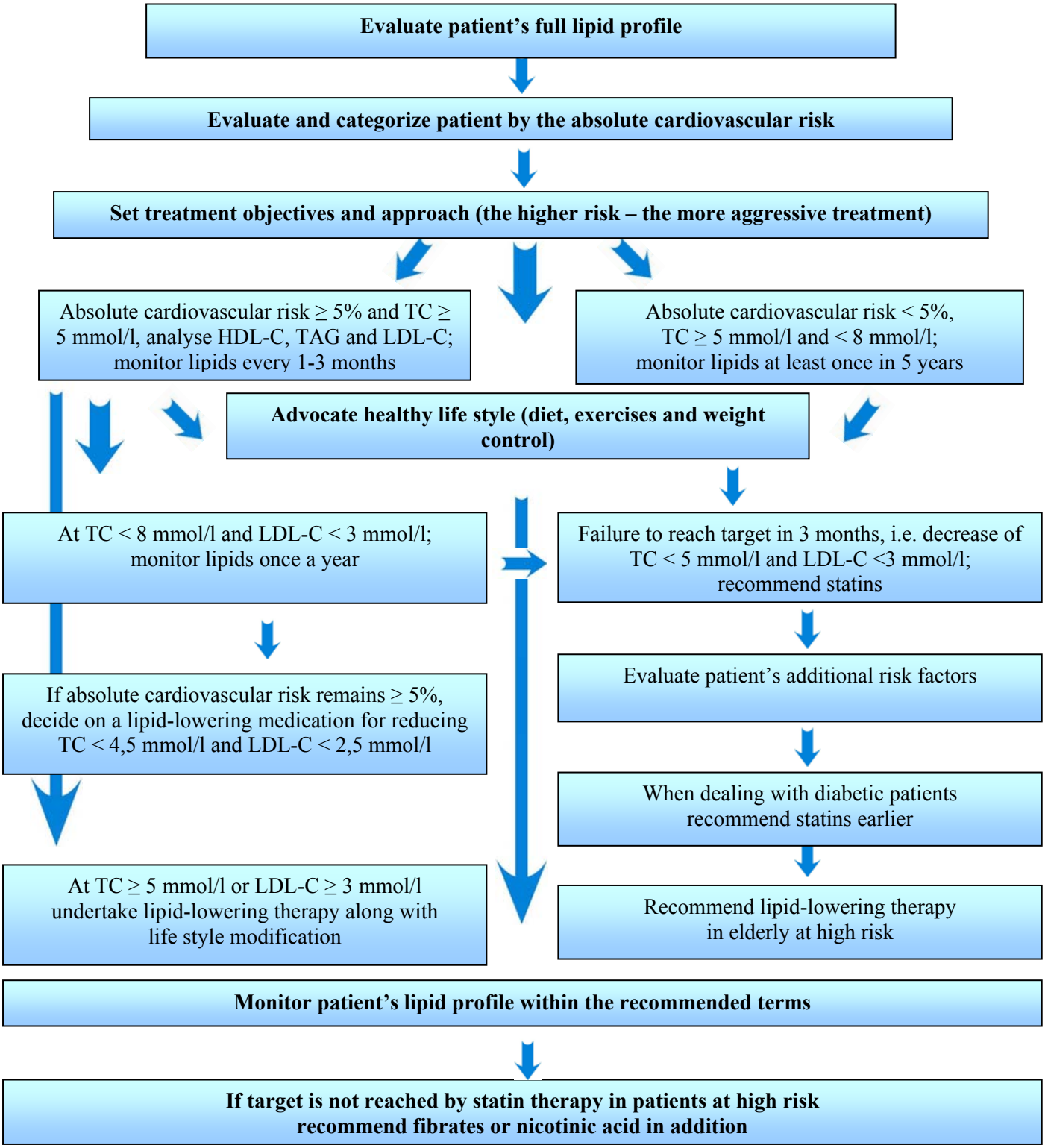
Lipid-Lowering Drugs Doses	Lipid/ Lipoprotein Effects	Delayed Clinical Results	Adverse Effects	Contraindications
HMG-CoA reductase inhibitors (statins)	LDL-C ↓18%-55% HDL-C ↑ 5%-15% TG ↓ 7%-30%	decrease of cardiovascular diseases and general mortality	miopathy; raised liver enzymes	**Absolute**: pregnancy; acute or chronic liver diseases **Relative**: concomitant use of certain drugs [(1)]
fibrates	LDL-C ↓ 5%-20% (rise in patients with high TG) HDL-C ↑ 10%-20% TG ↓ 20%-50%	decrease of cardiovascular diseases and general mortality	dispepsy; cholelithiasis; miopathy	**Absolute:** severe renal diseases; severe liver diseases
nicotinic acid	LDL-C ↓ 5%-25% HDL-C ↑ 15%-35% TG ↓ 20%-50%	decrease of cardiovascular diseases and acute myocardial infarction mortality; probably general mortality	flush-reaction; hyperglycaemia; hyperuricaemia (or podagra); gastrointestinal disturbances; hepatotoxic effect	**Absolute:** chronic liver diseases; severe podagra **Relative:** diabetes mellitus; hyperuricaemia; peptic ulcer
bile binding resins (bile acid sequestrants)	LDL-C ↓15%-30% HDL-C ↑3%-5% TG ↑ or no change	decrease of cardiovascular diseases and acute myocardial infarction mortality	gastrointestinal disturbances; constipation; reduced absorption of other drugs	**Absolute:** dysbetalipoproteinaemia; TG > 4,5 mmol/l **Relative:** TAG > 2,3 mmol/l
omega-3-free fatty acids	LDL-C ↓ or ↑ TG ↓ 30%-50%	decrease of cardiovascular diseases and general mortality	fish taste; dispepsy; decreased fibrinogen; worsened thrombocyte aggregation; hyperglycaemia	**Absolute:** haematologic diseases with impaired coagulation **Relative:** caution – treatment with anticoagulants and diabetics
cholesterol-absorption inhibitor (ezetimib)	LDL-C ↓ 10%-20% HDL-C ↑ 1% - 3% TG ↓ 8%	decrease of cardiovascular diseases and acute myocardial infarction mortality	abdominal pins; fatigue	**Absolute**: active liver disease
combined agents (ezetimib and statin)		decrease of cardiovascular diseases and acute myocardial infarction mortality	miopathy; abdominal pain; raised liver enzymes	**Absolute:** acute or chronic liver diseases **Relative:** combined use of certain drugs[(1)]

[(1)]*Cyclosporine, Gemfibrozil, macrolida, different antimicotic agents and cytochrome P450 inhibitors*

V. ALGORITHM FOR THE MANAGEMENT OF DYSLIPIDAEMIAS

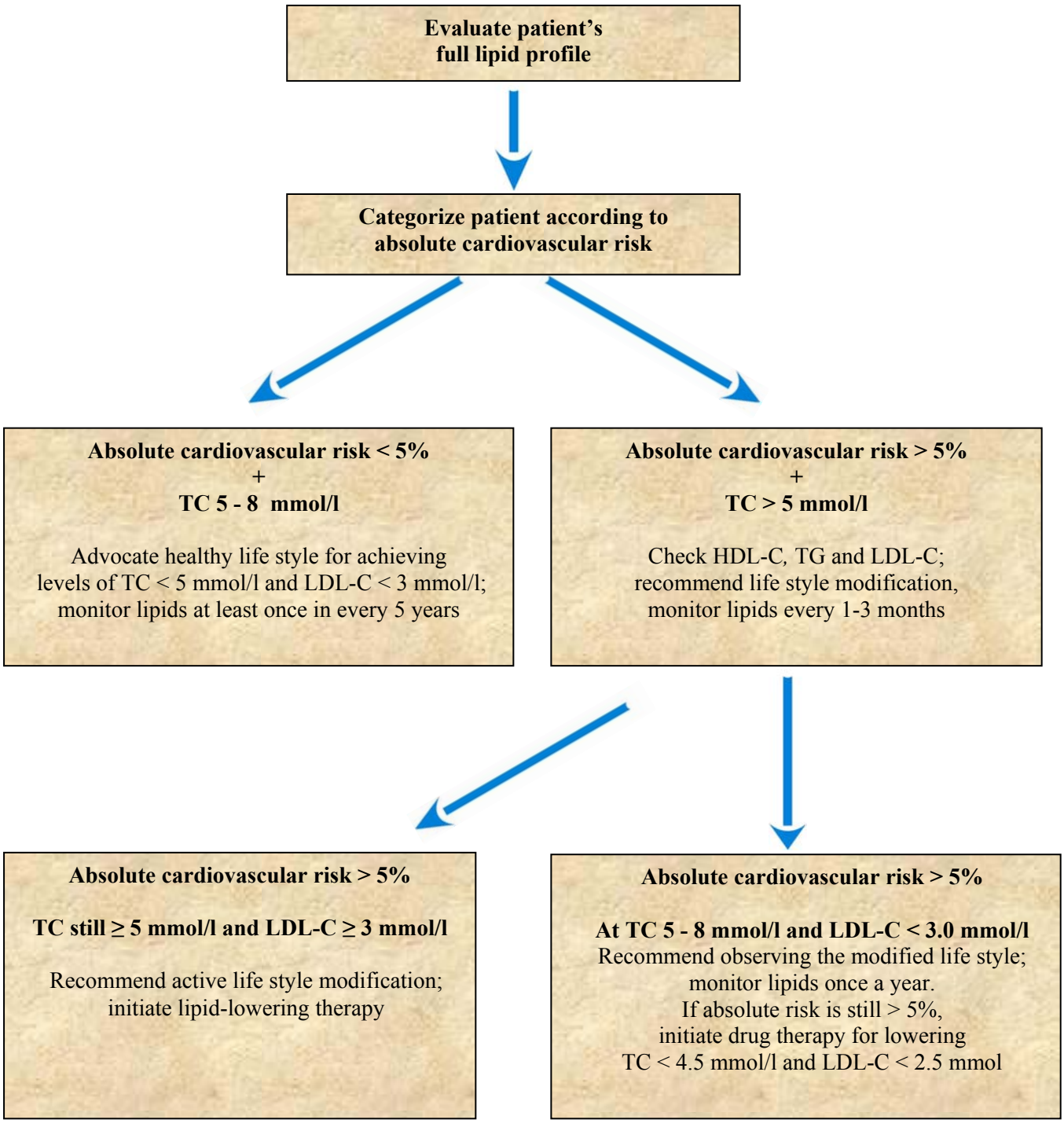
In common medical practice after the diagnosis "dyslipidaemia" is established, and depending on the cardiovascular risk evaluation, the doctor should make certain steps in a logical sequence. Different management programmes for atherosclerosis recommend different algorithms to be used by the general practitioner.

ADVANCED ALGORITHM FOR THE MANAGEMENT OF DYSLIPIDAEMIA FOR GENERAL PRACTITIONERS



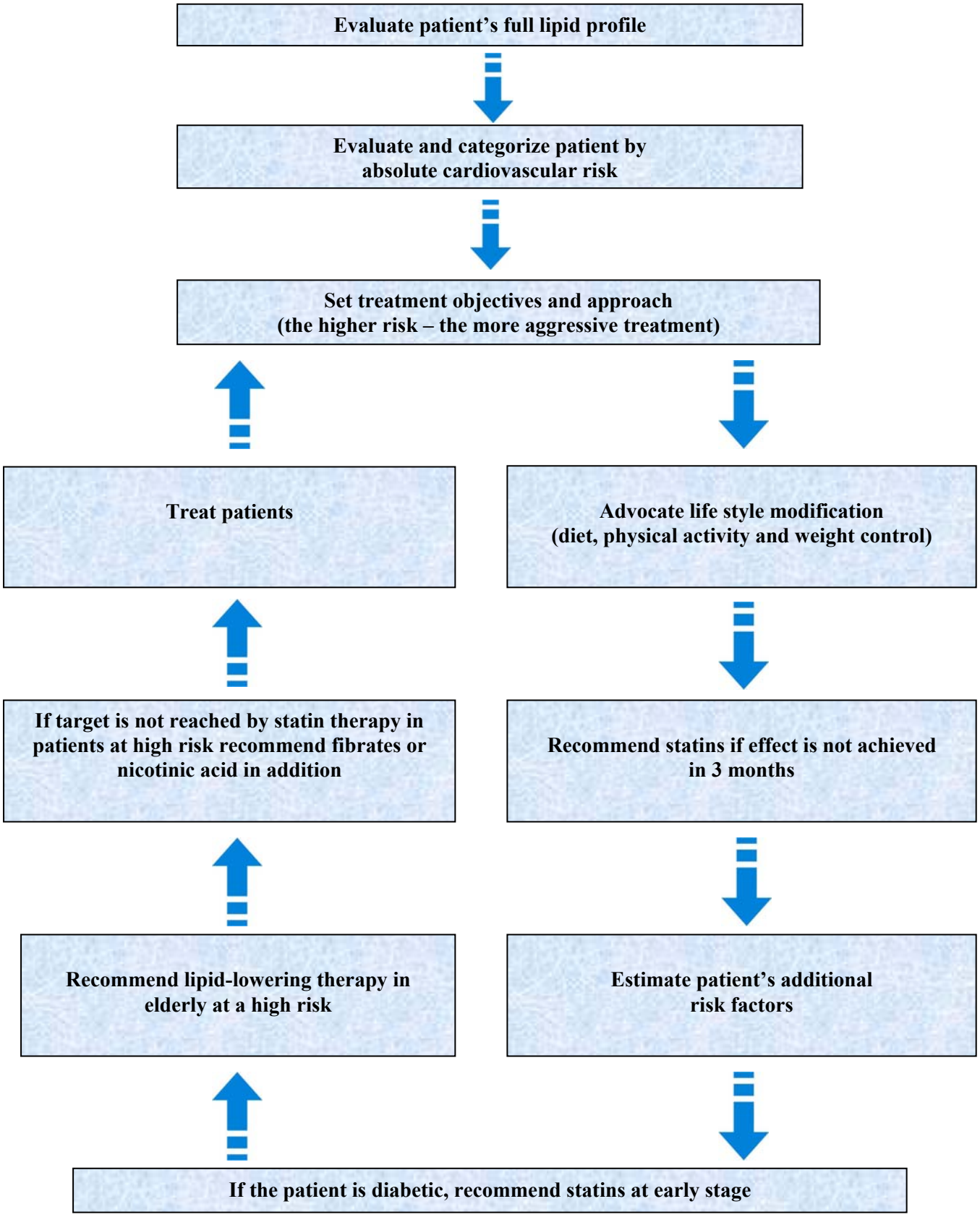
That algorithm can be simplified to enable the general practitioner promptly determine their approach in subjects with established dyslipidaemia.

BASIC ALGORITHM FOR THE MANAGEMENT OF DYSLIPIDAEMIA FOR GENERAL PRACTITIONERS



The logics in general practitioner's management of dyslipidaemia is presented in the form of consecutive steps, where they must follow the acts outlined in the advanced algorithm.

STEP ALGORITHM FOR THE MANAGEMENT OF DYSLIPIDAEMIA FOR GENERAL PRACTITIONERS



ANNEXES:

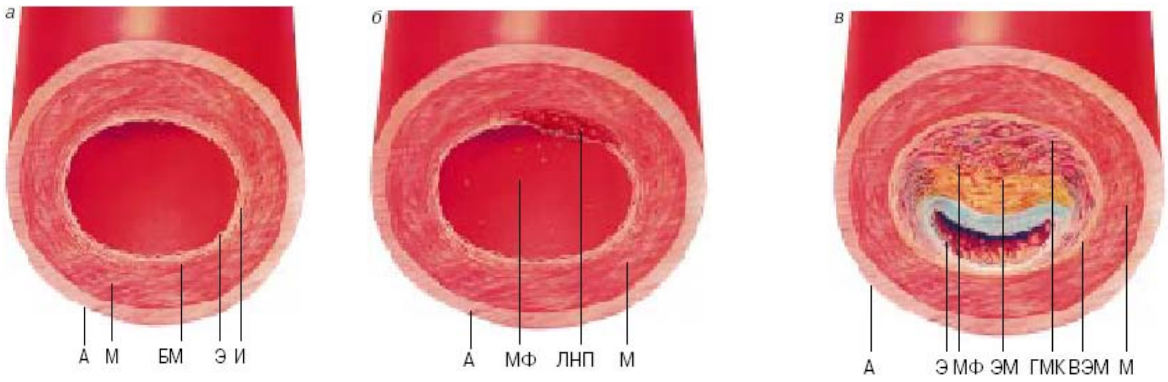
Annex No. 1

CHARACTERISTICS AND COMPOSITION OF PLASMA LIPOPROTEINS

Type	d (nm)	Density	COMPOSITION						
			Protein %	Lipids %	% of total lipids				
					TG	PHL	CE	C	FFA
Chilomicrons	90-1000	<0.95	1-2	98-99	88	8	3	1	…
VLDL	30-90	0.95-1.006	7-10	90-93	56	20	15	8	1
IDL	25-30	1.006 - 1.019	11	89	29	26	34	9	1
LDL	20-25	1.019 - 1.063	21	79	13	28	48	10	1
HDL	7.5-20	1.063 - 1.210	45-55	2-7	26-32	15 - 20	6-10	>6	

Annex No. 2

SCHEMATIC STRUCTURE OF ATHEROSCLEROTIC PLAQUE IN ARTERIES



a – normal arterial wall
E *– surface endothelium cells of the vessel wall;* ***M*** *– muscle layer (media);* ***A*** *– outer layer – adventitia;* ***И*** *– intima space*

b – arterial wall with a lipid strip
Macrophages ***(MF)*** *conglomerate under the endothelium layer, followed by formation of lipid deposits* ***LDL*** *and* ***VLDL***

c – arterial wall with stenosing atherosclerotic plaque
MF *– macrophages with lipid deposits;* ***SMS*** *– smooth muscle cells in the intima;* ***EM*** *– extracellular matrix;* ***IEM*** *– intravascular elastic membrane*

Annex No. 3

CARDIOVASCULAR RISK PREDICTION SCORE (by Framingham)

A. 10-YEAR RISK PREDICTION IN MEN

AGE (YEARS)	SCORE
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Score

Total Cholesterol (mg/l)	mmol/l	Age (years) 20 – 39	Age (years) 40 – 49	Age (years) 50 – 59	Age (years) 60 – 69	Age (years) 70 – 79
<160	<4.14	0	0	0	0	0
160-199	4.14-5.15	4	3	2	1	0
200-239	5.17-6.1	7	5	3	1	0
240-279	6.2-7.2	9	6	4	2	1
≥280	≥7.24	11	8	5	3	1

Score

	Age (years) 20 – 39	Age (years) 40 – 49	Age (years) 50 – 59	Age (years) 60 – 69	Age (years) 70 – 79
Non-Smokers	0	0	0	0	0
Smokers	8	5	3	1	1

HDL (mg/l)	mmol/l	Score
≥60	≥1.55	-1
50-59	1.29-1.52	0
40-49	1.03-1.27	1
<40	<1.03	2

Systolic Blood Pressure (mmHg)	Untreated Subjects	Treated Subjects
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

TOTAL SCORE	10-YEAR RISK (%)
< 0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥ 17	≥ 30

B. 10-YEAR RISK PREDICTION IN WOMEN

AGE (YEARS)	SCORE
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Score

Total Cholesterol (mg/l)	**mmol/l**	**Age (years) 20 – 39**	**Age (years) 40 – 49**	**Age (years) 50 – 59**	**Age (years) 60 – 69**	**Age (years) 70 – 79**
<160	<4.14	0	0	0	0	0
160-199	4.14-5.15	4	3	2	1	1
200-239	5.17-6.1	8	6	4	2	1
240-279	6.2-7.2	11	8	5	3	2
≥280	≥7.24	13	10	7	4	2

Score

	Age (years) 20 – 39	**Age (years) 40 – 49**	**Age (years) 50 – 59**	**Age (years) 60 – 69**	**Age (years) 70 – 79**
Non-Smokers	0	0	0	0	0
Smokers	9	7	4	2	1

HDL (mg/l)	**mmol/l**	**Score**
≥60	≥1.55	-1
50-59	1.29-1.52	0
40-49	1.03-1.27	1
<40	<1.03	2

Systolic Blood Pressure (mmHg)	**Untreated Subjects**	**Treated Subjects**
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

TOTAL SCORE	**10-YEAR RISK (%)**
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥ 25	≥ 30

Annex No. 4

MANAGEMENT OF ASYMPTOMATIC PATIENTS WITH DYSLIPIDAEMIA DEPENDING ON THE ABSOLUTE CARDIO-VASCULAR RISK (PRIMARY PREVENTION)

Total Risk < 5%	**Total risk > 5%**
TC < 5 mmol/l	**TC > 5 mmol/l**
Management: • Advise on life style modification; • Maintain TC bellow 5 mmol/l; • Monitor at least every 5 years.	**Management:** • Measure TC, HDL-C and TG – a fasting sample is required; • Measure LDL-C; • Recommend life style modification for at least 3 months; • Follow-up.
Objective: **TC < 5 mmol/l** or **LDL-C < 3 mmol/l**	**RESULT 1:** **TC > 5 mmol/l** and **LDL-C > 3 mmol/l**
	Management: • Abiding by the modified life style; • Initiation of lipid-lowering medication; • Monitor every 3 months.
	RESULT 2: **TC 5 - 8 mmol/L** and **LDL-C < 3.0 mmol/L**
	Management: • Advise on life style modification; • Annual control; • If total risk remains > 5% initiate lipid-lowering drugs until achieving TC < 4.5 mmol/l and LDL-C < 2.5 mmol/l.

Annex No. 5

CHOLESTEROL CONTENT IN DIFFERENT FOODS (mg/100g)

Product (100 g)	**Cholesterol (mg)**
Brain	2200-2800
Egg yolk	460
Liver	320
Heart	210
Cheese	160
Beef	125
Pork	300
Poultry	90
Fish	50
Milk (100 ml)	12

Annex No. 6

RELATIVE SHARE (%) OF CALORIES IN DIFFERENT FOODS IN THE DIET IN DYSLIPIDAEMIA

Nutritive Component	Recommended Intake
Saturated fats	< 7% of total calories
Polyunsaturated fats	Up to 10% of total calories
Monounsaturated fats	Up to 20% of total calories
Total fats	25% - 35% of total calories
Carbohydrates	50% - 60% of total calories
Proteins	Around 15% of total calories
Cholesterol	< 200 mg/d

Annex No. 7

BASIC GROUPS OF DRUGS ALLOWED FOR USE IN OUR COUNTRY FOR TREATMENT OF DYSLIPIDAEMIA AND RECOMMENDED DAILY DOSES

A. DRUGS:

I. STATINS

Atorvastatin – film tabl. 10 mg, 20 mg, 40 mg (scat. – nr. 30)

Simvastatin – film tabl. 10 mg, 20 mg (scat. – nr. 14 and 28), film tabl. 40mg (scat. – nr. 14 and 28), film tabl. 80mg

Rosuvastatin – film tabl. 20 mg (scat. – nr. 28)

Pravastatin – tabl. 10 mg, 20 mg (scat. – nr. 30)

Lovastatin – tabl. 20 mg, 40 mg (scat. – nr. 14, 28 and 30), tabl. 80 mg (scat. – nr. 14 and 28)

Fluvastatin - caps. 40 mg (scat. – nr. 28)

Fluvastatin XL depo-tabl. 80 mg (scat. – nr. 28)

II. FIBRATES

Gemfibrozil – caps. 300 mg, 450 mg, 600 mg (scat. – nr. 50)

Fenofibrate – caps. 67 mg (scat. – nr. 30), 100 mg (scat. – nr. 50)

Fenofibrate 200 M (micronised) 200 mg (scat. – nr. 30 and 50)

Bezafibrate – tabl. 200 mg

Cipofibrate - caps. 100 mg (scat. – nr. 30)

III. POLYUNSATURATED FREE FATTY ACIDS (OMEGA-3-FREE FATTY ACIDS)

Caps. Fish oil

Escimo-3 – caps. 500 mg, flac. 105 ml

Omacor – tabl. 1000 mg

Olisalvin - Omega – 3 Forte, caps. 1 g

Olisalvin – Omega - 3, caps. 300 mg

IV. BILE BINDING RESINS (BILE ACID SEQUESTRANTS)
Cholestyramine – pulvis 4 g/ packet

Colestipol – pulvis 5 g/ packet

Colesevelam - pulvis 1,3 g/ packet

V. NICOTINIC ACIDS AND DERIVATES
Nicotinic acid – tabl. 40 mg (scat. – nr. 40), amp. 10 mg/1 ml and 40 mg/2 ml

Acipimox – caps. 250 mg (scat. – nr. 30)

VI. CHOLESTEROL ABSORPTION INHIBITOR (EZETIMIB)
Ezetrol – tabl. 10 mg (scat. – nr. 14 and 28)

Vytorin – Ezetimibe 10 mg, combined with Simvastatin 20 mg, tabl.

VII. ANTIOXIDANTS
Probucol – tabl. 250 mg

VIII. OTHER DRUGS
Pectin – tabl. 500 mg, pulvis 10 g

Pectivit C – tabl. (scat. – nr. 60)

Lecithin – gran. 50 g, caps. 1g

Neolipidra – tabl. 300 mg

B. RECOMMENDED DAILY DOSES:

Atorvastatin (10 - 80 mg), **Simvastatin** (10 - 40 mg), **Rosuvastatin** (5 - 40 mg), **Pravastatin** (10 - 40 mg), **Fluvastatin** (40 - 80 mg), **Lovastatin** (20 - 80 mg)

Gemfibrozil (600 mg 2 times daily), **Fenofibrate** (200 mg)

Nicotinic acid (**Niacin**) with fast release (1,5 – 3 g)
Nicotinic acid with extended release (1 - 2 g) (**Niaspan**)
Nicotinic acid with sustained release (**OTC**) (1 – 2 g)
Nicotinic acid (300 mg)
Acipimox (250 mg 2-3 times daily)

Cholestyramine (4 - 16 g)
Colestipol (5 - 20 g)
Colesevelam (2,6 - 3,8g)

Fish oil – caps. (2-12g)
Escimo-3 (1,5- 4,5g = 5ml)
Omacor (1- 2g)
Olisalvin Omega–3 forte (1-2 g)
Olisalvin Omega–3 (300 mg)

Ezetimibe(10 mg)
Vytorin – (Ezetimibe 10 mg and Simvastatin 20 mg)

Reference: *McGowan M, LaRosa J., Weart C.* ***"Comprehensive lipid-lowering update: Part 2: Who needs lipid-lowering drugs?".*** *Patient Care* **,** *Originally published: March 1, 2006*

Annex No. 8

STEPS FOR REDUCING THE RISK OF MUSCLE TOXICITY
IN COMBINED FIBRATE – STATIN THERAPY

- Use statin monotherapy to achieve target levels of non-HDL-cholesterol
- Give preference to fish oil (omega-3 fatty acids) or nicotinic acid
- Keep the statin and fibrate doses low
- Prescribe fibrate at lunch after a meal, and statin – at night
- Avoid or use with caution the combination in renal dysfunction
- Make sure no other drug interaction takes place
- Train patient to detect muscle symptoms (muscle pain, weakness)
- Discontinue therapy if muscle symptoms and more than 10-fold raise of creatine kinase are present

non-HDL-cholesterol –

Annex No. 9

GENERAL RECOMMENDATIONS FOR LIPID-LOWERING THERAPY

1. **Before initiating lipid-lowering therapy have the following levels checked:**

- Liver enzymes (ASAT, ALAT, GGT, ALP) and CPK
- Blood glucose, uric acid, albumiuria

2. **Monitor enzymes during the first 12 months.**
3. **After stable condition has established control examinations and laboratory tests are recommended every 3, 6 and even 12 months, depending on patient's risk factors.**
4. **Recommendations for statin treatment:**

1) Start statin treatment on a not-working day in order to avoid muscle pain of another character/ origin.
2) Start statin treatment at a low dose and gradually increase it to moderate.
3) In failure to achieve effect try a different statin (the response is individual).
4) Recommend the drug be taken at night (exemptions are Atorvastatin, Rosuvastatin and Fluvastatin XL), for they have a longer semi-life and can be taken either during day or at night, with or without food).
5) Administer aspirin, provided no contraindications are available, as it might relief probable myalgia.
6) Try an alternative (e.g. daily) statin administration.

7) In dyslipidaemia with raised LDL-C and TG it is advisable that triglycerides are decreased first, then LDL-C-lowering therapy be initiated.

5. Recommendations for nicotinic acid treatment:

1) Start nicotinic acid treatment at a low dose and gradually titrate it.
2) Do not increase the dose fast.
3) Let patient decide on increasing the dose, since they feel best their tolerance.
4) Do not exceed a daily dose of 3 g.
5) If aspirin is taken ½ hour before nicotinic acid the flush can be diminished through prostaglandine blocking.
6) Aspirin is recommended at a higher than the preventive one dose, i.e. 1 tablet of 325mg.
7) It is advisable that nicotinic acid is taken during breakfast with view to retarded absorption and diminished flush.
8) Spicy foods and hot liquids are not recommended immediately before and after the nicotinic acid take.
9) A hot shower is not recommended immediately after the drug take.
10) The longer the drug is taken the fewer the flush episodes become.
11) Alleviation of itching is probable if sustained-release form of nicotinic acid is administered in combination with an antihistamin agent (Diphenhydramine).

6. Types of lipid-lowering statin therapy:

- ***Monotherapy*** – low or moderate doses of statins of first choice, reducing LDL-C by 30% - 40%.
- ***Aggressive*** lipid-lowering therapy (monotherapy with statins at high doses or combination of other lipid-reducing drugs), reducing LDL-C by up to 55%. It is indicated in the following cases:

✓ moderate monotherapy with statins fails to reach the target LDL-C level;
✓ very high initial level of LDL-C is established;
✓ tdisease progresses regardless of the lipid-lowering strategies;
✓ recently undergone acute coronary event.

7. Combined lipid-reducing therapy:

✓ if the effect of monotherapy with statin is insufficient (the target LDL-C level is not achieved);
✓ in case of patient's intolerance, toxicity or side effects, which require reducing the statin dose;

- ✓ if other lipid parametres are pursued (e.g. decreasing TG, raising HDL-C etc.);
- ✓ if combination of several lipid-lowering drugs with additive mechanism of action and additional effects upon the coronary risk reduction is likely to produce benefit.

8. Feasible combinations:

- Ezetimibe and statins;
- bile binding resins (bile acid sequestrants) and statins;
- fibrates and statins;
- omega-fatty acids (fish oil) and statins;
- fibers or vegetable stanoles and statins;
- nicotinic acids and statins.

9. Unacceptable combinations:

- ✓ Simvastatin, Atorvastatin and Lovastatin with Amiodarone, macrolides, calcium antagonists (Diltiazem, Amlodipine, Verapamil and Nifedipine), antiretrovirus agents, azole antimicotic agents etc. Pravastatin and Fluvastatin can be combined with the above drugs, because of their different metabolic pathways.

Annex No. 10

SPECIAL GROUPS PATIENTS TREATED FOR DYSLIPIDAEMIA

A. TREATMENT OF CHILDREN:

- lower doses, which ensures side effects;
- administration of bile acid sequestrants (resins) and certain statins at lower doses.

B. TREATMENT OF YOUNG ADULTS ***(up to 35 years):***

- only at the condition that LDL-C is above 3.36 mmol/l;
- life style modification;
- lipid-lowering therapy is discussed only in smokers and those having their LDL-C levels within 4.14 - 4.89 mmol/l;
- if LDL-C is higher they are regarded as adults.

C. TREATMENT OF ADULTS ***(over 64 for men and above 74 for women):***

- life style modification;
- lipid-lowering therapy even in subjects in their late 80s;
- due to the patients' advanced age there exists an increased risk of rabdomiolisis, therefore gradual titration of the lipid-lowering dose is advisable.

D. TREATMENT OF WOMEN:

- statins are absolutely contraindicated in women who are, or are likely to get pregnant;
- the rest of women are regarded as men with dyslipidaemia;
- in menopause subjects lipid status monitoring is recommended every 6 - 12 months.

Annex No. 11

ABNORMAL LIPID LEVELS IN SECONDARY DYSLIPIDAEMIA

CAUSE	TC and LDL	HDL-C	TG
Diabetes mellitus		↓	↑
Obesity	↑	↓	↑
Chronic alcoholism			↑
Chronic liver diseases			↑
Hypothyreoidism	↑		
Chronic Renal Failure			↑
Nephritic syndrome	↑		↑
Cholelithiasis	↑		
Bulimia			↑
Anorexia nervosa	↑		
Pancreatitis			↑
Hypoparathyreoidism	↑		↑
Podagra	↑		↑
Acromegaly, Cushing syndrome, glicogenoses, progeria			↑
Acute intermittent porphyria	↑		
Idiopathic hypercalciaemia	↑		↑
Pregnancy			↑
Lupus erythematosus	↑		↑
Myeloma multiplex	↑		↑
Antihypertensive medication: - thiazide diuretics, chlortalidone - furosemide, spironolactone - nonselective beta-blockers	 ↑ ↑	 ↓ ↓	 ↑ ↑ ↑
Retinoides	↑	↓	↑
Alopurinol, benzodiazepine derivates		↓	↑
Prednisolone	↑	↓	↑
Cimetidin		↓	
Anabole steroids		↓	

Annex No. 12

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