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Correction of hypertriglyceridemia in order to reduce the residual risk in atherosclerosis-related diseases. Expert Council Opinion

Russian Society of Cardiology, Russian Scientific Medical Society of Therapists, Eurasian Association of Therapists, Russian National Atherosclerosis Society, Russian Association of Endocrinologists, National League of Cardiologic Genetics

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In opinion the Expert council provides management tactics for patients with hypertriglyceridemia (HTG). It is demonstrated that HTG is a common condition in overweight patients and is an important component of residual risk. HTG creates additional conditions for the progression of atherosclerosis, so the level of triglycerides (TG) is recommended to be measured in patients with a high, very high and extremely high risk level. An indication for the appointment of drugs that reduce the concentration of TG is its level of more than 2,3 mmol/L. Statins are the agents of choice to reduce the risk of cardiovascular disease in high-risk patients with hypercholesterolemia and HTG. Fenofibrate is used to correct HTG, and in case of intolerance to it or when the target level of TG is not reached, omega-3 ethers of polyunsaturated fatty acids in a dose of 2-4 g/day are recommended. In patients with HTG with a TG level >5,6 mmol/L, fenofibrate is the agent of choice.

Key words: hypertriglyceridemia, fenofibrate, omega-3 PUFAs, cardiovascular disease, residual risk of cardiovascular complications.

Conflicts of Interest: nothing to declare.

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An expert meeting was held on February 15, 2019 in St. Petersburg on the topic "The use of fibrates and omega-3 polyunsaturated fatty acids (PUFAs) in the treatment of atherogenic mixed dyslipidemia". Its purpose was to discuss and develop a joint expert position on dyslipidemia problems, residual risk and treatment approaches.

Urgency of the issue

Coronary artery disease (CAD) remains the leading cause of death in all developed countries. Cardiovascular mortality is far ahead of mortality from infectious and oncological diseases. According to WHO estimates, by 2030 about 23,6 million people will die from cardiovascular diseases (CVDs) every year [1].

According to various sources, the annual total frequency of deaths is 1,2-2,4%, while the frequency of deaths from CVDs is 0,6-1,4%, and the frequency of non-fatal myocardial infarction (MI) is from 0,6% (according to the RITA-2 study) to 2,7% (according to COURAGE) [2-8]. In very high-risk patients, the annual death rate increases to 3,8%, while in patients with hemodynamically insignificant coronary artery atherosclerosis, it is 0,63% (according to REACH register) [9].

According to the SWEDEHEART study, after the use of new therapeutic methods, such as percutaneous coronary intervention (PCI), dual antiplatelet therapy, statins and angiotensin converting enzyme inhibitors (ACEs), from 1995 to 2009 there was a significant decrease in annual mortality due to MI from 25% to 15%.

However, over the past 6-8 years, the mortality rate has leveled off and remains unchanged [10]. In this regard, the search for additional opportunities to reduce the risk of cardiovascular complications (CVC) and the progression of atherosclerosis is relevant.

Residual risk and its association with triglycerides

Recently, it has become apparent that even when the target level of low-density lipoprotein cholesterol (LDL-C) is reached, patients still have a residual risk of CVC. Important reasons for the residual risk are high levels of triglycerides (TG) and low levels of high density lipoprotein cholesterol (HDL-C) in the blood plasma.

Thus, according to the Framingham Study, a TG level of >1,7 mmol/L is associated with significantly higher risk of CVC [11]. For example, even when the target level (TL) of LDL-C is reached (<1,8 mmol/L), CVC risk in patients with HDL-C <1,0 mmol/L is 64% higher than in patients with HDL-C ⩾1,4 mmol/L [12]. Elevated levels of TG and low levels of HDL-C synergistically increase the risk of cardiovascular events in patients with already reached of LDL-C TL (<2,1 mmol/L) [13]. It has been shown that in patients with a TG >2,3 mmol/L and, at the same time, HDL-C <0,8 mmol/L, the risk of CVC increases by 10 times compared with patients with normal values of TG and HDL-C [13, 14].

The scientific communities differently define hypertriglyceridemia (HTG) and severe HTG. Despite the epidemiological data on an increase in cardiovascular risk with an increase in TG levels >1,7 mmol/L, nevertheless, clinical studies of drug therapy confirm its effectiveness in patients with TG levels >2,3 mmol/L. According to NCEP ATP III, the normal TG value is determined by a level of less than 1,7 mmol/L, the borderline high — from 1,7 to 2,3 mmol/L, and the HTG is from 2,3 to 5,6 mmol/L, severe HTG >5,6 mmol/L [15]. Russian and European guidelines 2016 recommend starting drug therapy at a TG level >2,3 mmol/L in high-risk patients [16, 17]. In view of this, we consider it appropriate to start drug treatment of patients at a level of >2,3 mmol/L with a TL of TG <1,7 mmol/L. TG level in the range of 1,7-2,3 mmol/L requires non-drug correction.

Among the primary reasons of TG increase are hereditary mechanisms (increase of very low-density lipoproteins (VLDL) production, TG hydrolysis defect, defect in clearance of TG remnants in the liver). In this case, acute pancreatitis is the leading clinical manifestation of familial HTG [18].

A modern clinician should have an idea that secondary HTG is much more common than primary and can be caused, first of all, by insulin resistance and related conditions: type 2 diabetes mellitus (DM), metabolic syndrome and obesity. In this case, a characteristic manifestation of dyslipidemia, along with a high LDL level, is high level of TG and VLDL, as well as a low level of HDL. This condition is called combined dyslipidemia [14]. Combined dyslipidemia is an extremely common condition, and its significance is usually underestimated by clinicians. According to the NHAMES study, it is observed in 62% of CVD patients [19].

Among 22,063 patients receiving statin monotherapy in Europe and Canada, increased levels of TG and decreased levels of HDL-C were observed in 38,8% and 26%, respectively [20]. Other reasons for increasing of TG levels may include chronic kidney disease, hypothyroidism, alcohol abuse, systemic lupus erythematosus, and the use of antiretroviral drugs and corticosteroids [21].

The predominant mechanism underlying the atherosclerotic process in HTG is the overproduction of VLDL in the liver. It was noted that in atherogenic combined dyslipidemia, the transfer of TG from VLDL to LDL and, at the same time, the transfer of

cholesterol esters from LDL to VLDL occur. An additional pathway for atherogenesis appears: VLDL, which lost part of the TG in exchange for cholesterol, become smaller, which significantly increases their atherogenicity (the ability to penetrate the vessel wall) [22]. In addition, in patients with atherogenic combined dyslipidemia, the level of small dense low-density lipoproteins (sdLDL) is increased. It penetrate the vascular wall even more easily due to their small size, are more susceptible to peroxidation, more often retained in the vascular wall, and contribute to the development of endothelial dysfunctions. Due to increase of thromboxane synthesis, it increase platelet activity, do not bind to liver receptors and, therefore, are more slowly excreted from the bloodstream, leading to an acceleration of atherogenesis [22, 23].

In this regard, in patients with obesity and type 2 DM, non-HDL cholesterol (non-HDL cholesterol=TC-HDL) gives much more information for cardiovascular risk assessing [24]. According to some studies, non-HDL cholesterol has a higher level of prognostic significance compared with LDL in patients with metabolic syndrome and DM [25]. International guidelines propose considering non-HDL cholesterol as a secondary aim after reaching the LDL TL [15, 26].

For quite a long time, despite the availability of a large amount of epidemiological data on the contribution of a high TG level to the atherosclerotic process, there was no convincing evidence that with TG decrease there is a decrease in cardiovascular events rate. The line was drawn under the role of TG in atherogenesis by the ACCORD-LIPID (subanalysis of the data of patients with elevated TG levels) and the REDUCE-IT studies, the results of which will be discussed below [27, 28].

Approaches to the HTG treatment and atherogenic combined dyslipidemia

LDL is the most atherogenic plasma particles, and as a result, treatment of a patient with dyslipidemia should begin with drugs aimed to reducing this particular parameter — HMG-CoA reductase inhibitors (statins). Second-line drugs designed to achieve LDL target level are cholesterol absorption inhibitors (ezetimibe) and PCSK9 inhibitors (evolocumab, alirocoumab).

If an elevated TG level is detected (>5,6 mmol/L), it is recommended to start fenofibrate therapy. At a TG level of 2,3-5,6 mmol/L, drugs aimed at TG lowering should be combined with statin therapy: fibrates (fibroic acid derivatives) and omega-3 PUFA ethyl esters.

The mechanism of action of fibrates is the activation of peroxisome proliferator-activated receptor alpha (PPARα). These receptors are located in the liver, muscles, adipose tissue, heart, kidneys, macrophages and platelets.

The main role of PPARα receptors is to regulate the metabolism of lipids and lipoproteins, inflammation and endothelial function. Activated PPARα receptors bind to specific DNA sites, stimulating or inhibiting the main genes encoding metabolic processes. It should be noted that from the class of fibrates, only fenofibrate can be used in combination with statins [17, 29].

Fenofibrate increases the synthesis of ApoA1, ApoA2, the activity of lipoprotein lipases, and reduces the synthesis of ApoC III, ApoB100 and the concentration of sdLDL. Correspondingly, this leads to an increase in HDL-C by 10-30%, accelerated conversion of chylomicrons into their remnants, a decrease in LDL-C by 25%, sdLDL — by 50%, and TG and VLDL synthesis reducing. TG levels can decrease on average up to 50% [30-32].

Table 1 shows the mechanisms of action and the comparative effectiveness of fenofibrate, statins and ezetimibe in terms of their effect on the lipid profile [15, 30, 33-35].

In addition to the effect on lipid metabolism, fenofibrate reduces the level of uric acid by an average of 25%, fibrinogen — by 21% and C-reactive protein — by 34% [30-32].

Clinical studies are important, proving the effects of fenofibrate therapy on surrogate and hard endpoints. One of the first studies in this category was the DAIS study, which showed the positive effects of micronized fenofibrate therapy at a dose of 200 mg/day on the size of the atherosclerotic plaque [36]. The results of the ACCORD and FIELD studies turned out to be even more significant [27, 37].

The first major study in patients with type 2 DM was the FIELD study [37, 38]. The aim of this randomized clinical trial was to evaluate the effect of fenofibrate intake on cardiovascular mortality in patients with type 2 DM (n=9,795). Inclusion criteria were: history of type 2 DM, age of 50-75 years, total cholesterol (TC) level from 3,0 to 6,5 mmol/L, ratio of TC/HDL-C levels ⩾4 or TG level from 1,0 to 5,0 mmol/L.

The primary endpoint was myocardial infarction (MI) or death due to CVC. Patients were randomized to 200 mg fenofibrate or placebo treatment groups, and the follow-up was 5 years on average. In the fenofibrate group compared with placebo, the number of cases of MI and cardiovascular death was reduced by 11%, although this difference was not statistically significant (P=0,16). However, in the fenofibrate group, the incidence of nonfatal MI significantly decreased by 24% (p=0,01), the number of cases of revascularization by 21% (p=0,035), there were also significantly lower number of CVC cases

Table 1

Comparison of the effectiveness of fenofibrate, statins and ezetimibe [adapted from 15, 30, 31, 33-35]

Mechanism of action	Fenofibrate	Statins	Ezetimibe
	PPARa activation leading to normalization of lipid metabolism	Inhibit HMG-CoA reductase, which is involved in the synthesis of cholesterol	Selectively inhibits the absorption of cholesterol and certain plant sterols in the intestine
LDL-C decrease [15]	5-20%	18-55%	15-30%
Triglycerides' decrease [15]	20-50%	7-30%	do not change
HDL increase [15]	10-20%	5-15%	3-5%
LDL particle size increase [28, 29]	50%	no	no

(p=0,003). However, the incidence of all-cause mortality, non-cardiovascular mortality and strokes did not significantly change. It should be noted that the study patients were allowed to use statins, and by the end of the study there was a disproportion in the number of patients who received it (17% in the placebo group and 8% in the fenofibrate group, p<0,0001). According to the authors, this fact could "blur" the result in the main group of the study [37, 38].

A further ACCORD Lipid study included 5518 patients with type 2 DM. Unlike the previous study, in this research all patients took simvastatin at a dose of 20-40 mg/day and were randomized to a 160 mg/day fenofibrate therapy group or placebo.

The follow-up was an average of 4,7 years. The primary endpoint is the first CVC (non-fatal MI, non-fatal stroke, cardiovascular death). The secondary endpoint is the difference in outcomes against the background of various treatment regimens, overall mortality, microvascular complications, quality of life, and efficiency-cost ratio. The primary endpoint reached: 2,4% of patients/year in the placebo group and 2,2% of patients/year in the fenofibrate group (risk ratio (RR) 0,92 (95% confidence interval (CI) 0,79-1,08), p=0,32). Cardiovascular mortality was 0,72% per year in the fenofibrate group and 0,83% per year in the placebo group (p=0,26). All-cause mortality was 1,47% per year in the fenofibrate group and 1,61% per year in the placebo group (p=0,33) [27]. The main result of the study was that fenofibrate therapy reduced macrovascular events (CVD risk) in the group of patients with atherogenic combined dyslipidemia (TG ⩾2,3 mmol/L and HDL cholesterol ⩽0,9 mmol/L) by 31% Moreover, the combination therapy with fenofibrate and simvastatin was well tolerated. Consequently, in the ACCORD study, cardiovascular risk remained elevated despite statin therapy, and was associated with HTG and decreased HDL-C level.

ACCORD Lipid results supported current guidelines for the treatment of lipid disorders: additionally prescribe drugs from the fibrate group to a patient taking statin monotherapy with a TG level >2,3 mmol/L.

The guidelines of ESC/EAS 2016 and the Russian National Society of Atherosclerosis 2017 for the management of dyslipidemias include the following non-drug methods for reducing TG: reduce overweight (body mass index (BMI) 20-25 kg/m2, waist circumference <94 cm (men) and <80 cm (women)), decrease alcohol consumption (patients with HTG should completely refuse alcohol), increase regular physical activity (exercise for at least 30 minutes every day), reduce the carbohydrates and salt intake (up to 5 g/day), increase the intake of omega-3 PUFAs, decrease the consumption of mono- and disaccharides, trans fats (<1% of total consumption) and saturated fats (<10% of total consumption), replace saturated fats with mono- and polyunsaturated [16, 17]. The management strategy for patients with combined dyslipidemia is presented below (Fig. 1).

Based on the developed common attitude, the Council of Experts proposes to clarify the medical methods for lowering of TG levels presented in the guidelines of ESC/EAS 2016 and the Russian National Society of Atherosclerosis 2017, namely: the possibility of prescribing omega-3 acid ethyl esters at a dose of 2-4 g/day in non-drug therapy futility at a TG level of 1,7-2,3 mmol/L, as well as in fenofibrate intolerance or in failure to achieve target TG level <1,7 mmol/L. It is also need to clarify practicability to add fenofibrate to statin therapy in patients of high, very high and extremely high risk, to determine whether fenofibrate as a first-line drug at a TG level of ⩾5,6 mmol/L (Table 2).

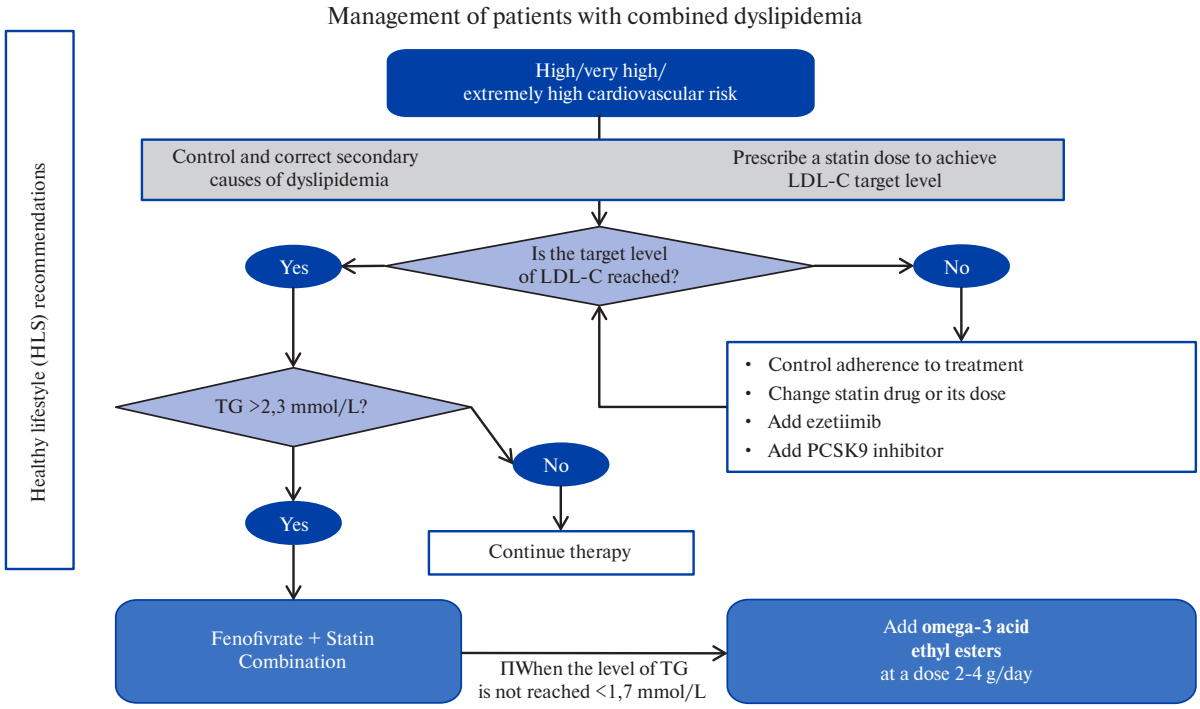

Fig. 1. Management of patients with combined dyslipidemia.

Omega-3 acid ethyl esters (Omacor) are second-line drugs using to reduce the TG level. Recently, a REDUCE-IT study involving 8 thousand patients was completed, which proved the effect of omega-3 PUFAs on hard endpoints [31]. Inclusion criteria were: a history of CVDs (~ 70% of patients) or type 2 DM+>1 RF, TG level ⩾2,3 mmol/L and <5,6 mmol/l, achieved LDL TL >1,03 mmol/L and ⩽2,6 mmol/L.

The primary endpoint was the time from randomization to the first event: cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, revascularization, unstable angina pectoris. A 25% reduction in the relative risk of major adverse cardiovascular events was demonstrated ($p<0,001$) in the group of patients taking omega-3 PUFAs (eicosapentaenoic acid 4 g/day) compared with placebo.

Thus, the treatment regimen for HTG can be represented as follows (Fig. 2).

Combination therapy of combined dyslipidemia with statins and fenofibrate has long been included in clinical practice and is recommended by international and Russian associations [16, 17]. In clinical studies, the effectiveness of fenofibrate was evaluated in combination with simvastatin [27], rosuvastatin [40, 41], atorvastatin [40] and pravastatin [42, 43]. The use of fenofibrate and statins combination made it possible to achieve the TL of LDL-C, non-HDL-C and TG 5 times more often compared with medium-dose statin monotherapy [44].

Due to the advisability of combination therapy using, safety data on the combined use of statins and fenofibrate deserve special attention. Fenofibrate is the only drug in this group that can be combined with statins. Fenofibrate, unlike statins, is metabolized by the action of uridining glucuronyl transferase (UGT), without the participation of cytochromes and their metabolic pathways do not cross. In view of this, the combined use of fenofibrate with various statins does not increase their plasma concentration and the area under the concentration-time curve (Cmax and AUC) [29]. It is known that combination therapy does not lead to a risk of myositis or rhabdomyolysis in comparison with statin monotherapy [27, 29]. In the ACCORD-Lipid study, the use of the combination of simvastatin and fenofibrate for 4,7 years did not increase the risk of myositis or rhabdomyolysis compared to simvastatin [27]. According to the FDA, the incidence of rhabdomyolysis when using the combination of statin-fibrate is 0,58 per 1 million patients. In clinical studies, in 3-4% of patients there may be increase of liver enzymes level 3 times higher than normal [29].

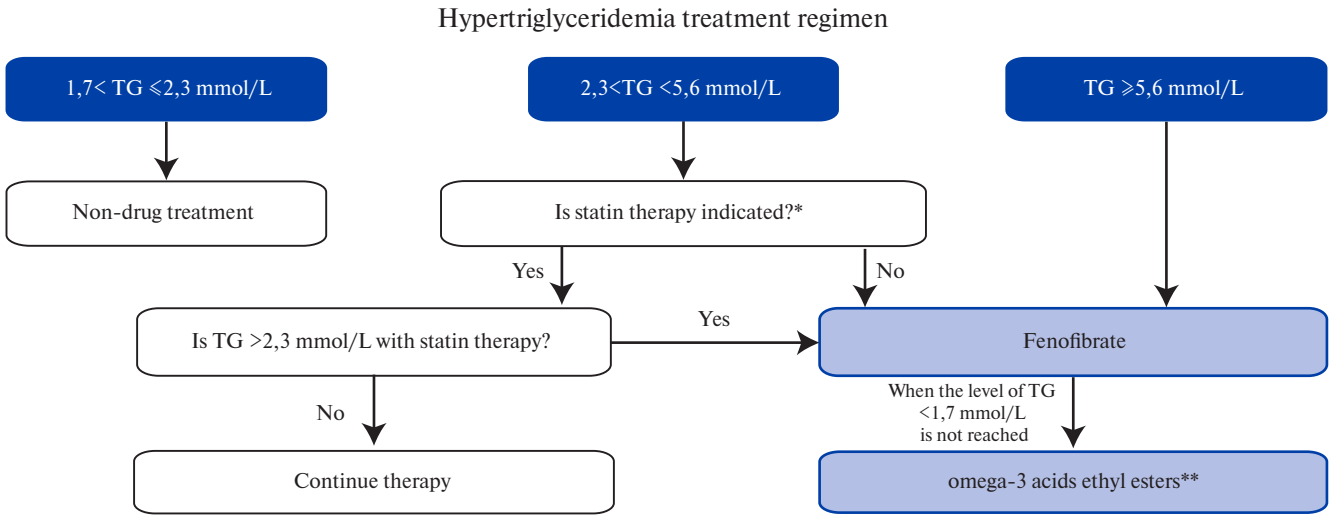

Fig. 2. Hypertriglyceridemia treatment regimen [adapted from 36-39].
Note: * — taking into account the clinical phenotype of the patient (hypercholesteremia), ** — omega-3 acids ethyl esters at a dose of 2-4 g/day. In severe hypertriglyceridemia, consider the use of plasmapheresis.

Table 2

Recommendations of the Council of Experts on the HTG treatment

At a TG level of 1,7-2,3 mmol/L, non-drug therapy should be performed. If there is no effect, consider omega-3 acids ethyl esters in a dose of 2-4 g/day.
Drug therapy should be started in patients with triglycerides >2,3 mmol/L
Statins are first-line drugs to reduce CVD risk in high-risk patients with hypercholesterolemia and hypertriglyceridemia
In patients of high, very high and extremely high risk with triglycerides level >2,3 mmol/L, despite the treatment with statins, fenofibrate should be added to therapy
In TG level of ⩾5,6 mmol/L, the priority is to prevent pancreatitis with the use of fenofibrate
In case of fenofibrate intolerance or if the target TG level (<1,7 mmol/L) is not reached, it is advisable to use omega-3 acids ethyl esters at a dose of 2-4 g/day.

It should be noted that combination of fenofibrate and various statins (simvastatin, atorvastatin, rosuvastatin) has been used for a sufficiently long period of time, and the risk-benefit ratio of this combination is certainly positive for patients with HTG [14, 29].

Conclusion

At a TG level above 2,3 mmol/L, phenofibrate or omega-3 acid ethyl esters should be added to strategy. HTG is most common in patients with obesity, insulin resistance, type 2 DM, metabolic syndrome, and chronic disease kidneys, as well as in alcohol abusers. HTG significantly complements the mechanisms that affect atherogenesis, which cannot be completely eliminated with the help of statins and ezetimibe. The Council of Experts considers it appropriate to increase the awareness of clinicians about the role of HTG in the pathogenesis of atherosclerosis, the importance of assessing the level of TG in patients with high, very high and extremely high cardiovascular risk in routine practice of general practitioners, cardiologists, therapists, endocrinologists and about possible treatment options. Recent data on the TG level as an independent risk factor for CVDs, along with LDL and TC, can contribute to the further study of methods for HTG correcting. Fenofibrate is the main drug in the strategy for lowering of TG levels in addition to statin therapy in patients with TG levels >2,3 mmol/L. The second-line drugs for TG level lowering are omega-3 acid ethyl esters in a dose of 2-4 g.

Conclusion. Management of patients with HTG

— In patients with a high, very high and extremely high risk of atherosclerosis-related CVDs and their

complications, it is necessary to measure the level of fasting TG;

— It is necessary to consider the possible causes of HTG and assess the total cardiovascular risk;

— To achieve target levels of LDL in accordance with the risk category; statins, ezetimibe, and PSCK9 inhibitors are designed to lower LDL;

— To reach the TG target level of <1,7 mmol/L; a decrease in TG is an important component in cardiovascular risk reducing;

— At a TG level of 1,7-2,3 mmol/L, non-drug therapy should be given;

— At a level of TG >2,3 mmol/L, fenofibrate must be prescribed for its correction;

— At a TG level of ⩾5,6 mmol/L, fenofibrate is first-line drug to prevent the development of pancreatitis;

— In case of fenofibrate intolerance or failure to reach the target level of TG <1,7 mmol/L, it is advisable to use omega-3 acids ethyl esters in a dose of 2-4 g/day.

Conflict of Interest: nothing to declare.

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