ДИСЛИПИДЕМИИ – СЪВРЕМЕННИ РАЗБИРАНИЯ И ПОВЕДЕНИЕ

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РЕЗЮМЕ
Сърдечно-съдовите заболявания (ССЗ) са основна причина за смърт и инвалидност у нас и по света. За развитието им основно значение има нарушението в липидния метаболизъм, което води до атеросклероза на съдовете. Дислипидемиите представляват всякакво нарушение в нивата и/или функцията на плазмените липопротеини. Те са семейство нарушения в липопротеиновия метаболизъм и са различни по вид и причина. Честотата им е висока в общата популация и сред пациентите със ССЗ. Разгледани са съвременните разбирания за развитието на дислипидемиите, които отчитат не само нивата на липопротеините, но и техния брой, форма, големина, както и други показатели на липидния метаболизъм. Посочени са съвременните препоръки за поведение при дислипидемия. Те включват комплексни мерки за промяна в начина на живот и храненето, както и приложението на различни лекарствени средства. Посочени са основните цели за лечение. В медикаментозното лечение се отбелязва водещата роля на статините за снижение на плазмените липиди. Посочени са и други класове медикаменти, както и съвременни експериментални начини за повлияне на дислипидемиите.

Ключови думи: дислипидемии, липопротеини, сърдечно-съдъво заболявания, статини

ВЪВЕДЕНИЕ

Сърдечно-съдовите заболявания (ССЗ) са основна причина за смърт и инвалидност – общо 16.7 млн. умират годишно по света от ССЗ, като ИБС е причина за фатален край при 7 млн., а летален мозъчен инсулт развиват около 6 млн. (1). Те засягат еднакво двата пола и са причина за смърт при 42% от жените и 38% от мъжете преди 75 години в Европа. Съмнеността от ССЗ се промяна в различните страни, но остава висока в Източна Европа и България (2). Освен като основна причина за смърт, ССЗ са и една от най-важните причини за инвалидност и за загуба на години активен живот, като в развитите икономически страни те

DYSLIPIDEMIAS – MODERN UNDERSTANDING AND MANAGEMENT

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ABSTRACT
Cardiovascular diseases (CVDs) are the major cause of mortality and disability in Bulgaria and worldwide. Lipid metabolism disorders have a major impact on their development and this leads to vascular atherosclerosis. Dyslipidemias are any disorder in the levels and/or the function of plasma lipoproteins. These represent a family of disturbances in the lipoprotein metabolism and are different in form and etiology. Their rate of occurrence is high in the general population and in patients with CVDs. The modern understanding of the development of dyslipidemias is overviewed. It takes into account not only the levels of the lipoproteins but also their number, form, size, as well as other indices of the lipid metabolism. The current guidelines on dyslipidemia management are discussed. They include complex measures for lifestyle and diet changes, as well as application of different classes of medications. The major targets for treatment are pointed out. The pivotal role of statins in plasma lipid reduction is stressed on. Other classes of medications are also mentioned, as well as up-to-date experimental methods for affecting dyslipidemias.

Keywords: dyslipidemia, lipoproteins, cardiovascular diseases, statins

INTRODUCTION
Cardiovascular diseases (CVDs) are the main reason for mortality and disability – each year a total of 16.7 million people worldwide die of CVDs with ischemic heart disease (IHD) being the cause of a lethal outcome for 7 million individuals, and lethal brain stroke is observed in 6 million patients (1). They affect both genders equally and are reason for death in 42% of the women and 38% of the men under 75 years of age in Europe. CVD mortality rate is different in the different countries but it remains high in Eastern Europe and Bulgaria (2). In addition to being a major reason for death, CVDs are also one of the main reasons for disability and loss of active years of life. In the economically developed coun-
се отговорни за около 10% от общата тежест на болестите, а в развиващите се тя достига до 86% (3). Това води до огромни икономически загуби, които са едновременно загуби на болния и близките му, загуби на държавата и здравната система и разходи на обществото от преждевременна загуба на продуктивност (1). За появата на ССЗ основно значение има атеросклерозата. Ролата на липидите в развитието на атеросклерозата е известна още от работата на Вирхов и колеги през 19 век върху морфологичните особености на атеросклеротичната плака и съдържанието на холестерол в нея, както и на Ignatowski, Anitchkow и колеги в началото на 20 век, които постигат по експериментален път атеросклероза при зайци след продължителен прием на богата на мазнини диета. Липопротеините са изключително важни елементи в развитието на атеросклерозата при хората и са съществени предиктори на риска от развитие на атеросклероза при индивиди от различни региони и общества. Ето защо всеки нарушение на липидната обмяна е от съществено значение за развитието и клинична изява на ССЗ.

ДЕФИНИЦИЯ И ЧЕСТОТА

Понятието дислипидемия включва всяко нарушение в нивата и/или функцията на плазмените липопротеини (4). Те могат самостоятелно или във взаимодействие с други сърдечно-съдови рискови фактори да участват в развитието на атеросклероза. Честотата на дислипидемиите по света е висока. В САЩ тя е около 53% (5), като при възрастни над 65 години нараства до 60% (6). Подобна честота на дислипидемиите е посочена и в Иран, където 66% от градското население е с някаква форма на нарушение на липопротеиновия метаболизъм (7). В условията на първична обща практика в Канада честотата на дислипидемията е била само 14% (8). В Европа обаче едва 35% от хората, които са регистрирани в общи лекарски практики на 8 страни, са били в границите на нормалните липидни показатели според изходните данни на проучването EUROAction (9). У нас, по данни от епидемиологичното проучване CINDI през 2002 г., с повишен ОХ над 6.2 mmol/l са около 25% от мъжете и около 30% от жените, но 62% от изследваните лица никога не са изследвали нивата на липидите си. Според резултатите от EUROASPIRE III честотата на ОХ>4.5 mmol/l у нас сред високорискови мъже и жени без ССЗ е трие they are responsible for about 10% of the total disease burden, and in the developing countries the percentage reaches 86% (3). This leads to significant economic losses, which are also losses for the patients and their families, losses for the country and the health system, as well as expenditure for society due to the premature loss of productivity (1).

Atherosclerosis has a major influence on the occurrence of CVDs. The role of lipids for the occurrence of atherosclerosis has been known from the work of Virchow and associates in the 19th century on the morphological specifics of atherosclerotic plaque and its cholesterol content, as well as from the work of Ignatowski, Anitchkow and colleagues from the beginning of the 20th century, who, for the first time, induced experimentally atherosclerosis in rabbits after a prolonged high-fat diet. Lipoproteins are vitally important elements in the development of atherosclerosis in individuals from different regions and societies. Therefore, each impairment of the lipid metabolism is of key importance for the development and clinical presentation of CVDs.

DEFINITON AND INCIDENCE

The term dyslipidemia includes each impairment in the levels and/or function of the plasma lipoproteins (4). They can, individually or in combination with other cardiovascular factors, participate in the development of atherosclerosis.

The incidence of dyslipidemias worldwide is high. In the US, it is about 53% (5) with it rising to 60% in the population aged over 65 (6). A similar incidence rate of dyslipidemias was determined in Iran where 66% of the urban population had some form of lipoprotein metabolism impairment (7). In primary general practice setting in Canada, the incidence of dyslipidemia was only 14% (8). In Europe, however, only 35% of the people registered in general practices in 8 countries, were within the limits of normal lipid indicators, based on data from the EUROAction trial (9).

In our country, data from the epidemiological trial CINDI from 2002 shows that 25% of men and about 30% of women are with elevated total cholesterol (TC) >6.2 mmol/L, but 62% of the studied patients had never had their lipid levels tested. According to the results from EUROASPIRE III the incidence rate of TC >4.5 mmol/L among high-risk males and females without CVD in our country is 86% (10).

Dyslipidemias include a wide spectrum of lipid disorders some of which are of significance in regard to CVD prevention. A great importance is assigned to the elevation of TC and low-density lipoproteins
86% (10).

Dyslipidemias include a wide spectrum of lipid disorders, each of which is defined by its unique features and pathophysiology. Onset of hyperlipidemia usually occurs before the development of clinical symptoms, which may be silent or develop slowly over time. The dyslipidemias can be either primary or secondary, mainly due to factors such as aging, age-related changes in lipid metabolism, and certain genetic factors.

**TYPES OF DYSLIPIDEMIAS**

LDL-cholesterol is a significant component of the total cholesterol content in the plasma. A high LDL cholesterol level is a primary risk factor for the development of cardiovascular diseases (CVDs), which are the leading cause of death worldwide.

LDL-cholesterol is responsible for transporting cholesterol from the liver to the peripheral tissues. It is primarily synthesized in the liver and the intestine, and its metabolism is influenced by genetic factors and environmental factors, such as diet and physical activity. The level of LDL cholesterol is determined by several factors, including the size and density of LDL particles, their apolipoprotein composition, and their ability to interact with other lipoproteins in the bloodstream.

In recent years, the presence of elevated lipoprotein(a) [Lp(a)] levels has started to attract attention as a predictor of cardiovascular risk. Lp(a) is a heterogeneous category of lipoproteins, which consists of 7 subtypes based on their molecular characteristics, size, and density. LDL-I is the largest particle with the lowest density, moving to LDL-IVB the size decreases and the density increases (11,12).

The presence of numerous small, dense LDL particles, known as phenotype B according to the Austin and Krauss classification (13), leads to proven higher IHD risk. It is also related to a subclinical presence of calcifications of the coronary vessels. This explains certain characteristics of the metabolism of the small, dense LDL particles: they spend more time in the plasma because it is more difficult for the lipoprotein lipase in the liver to clear them, they have higher oxidative properties, bind more easily to the arterial proteoglycans and have higher permeability through the endothelial barrier (14). Phenotype B is three times more frequent in males – 34% versus 11% (15). The protein concentration is also of significance in regard to the development of CVDs – these are apoproteins with two main classes A and B, as well as their ratio (15).

There is data that apoB plays an important role in calculating the cardiovascular risk (16) with apoB and the apoB/apoA ratio being better predicting factor than the LDL cholesterol levels in men and women part of a prospective study (17). The apoB/apoA ratio has been used as a measure of lipid dysmetabolism in the largest so far case-control study on acute myocardial infarction (AMI) – INTERHEART (18). Another indicator for LDL concentration is the number of LDL particles in the plasma (LDL-P). It is determined via MRI spectroscopy. Several studies show that LDL-P is a better predictor of CVDs than the level of LDL cholesterol (19,20). High LDL-P levels predict a higher CVD risk regardless of the LDL cholesterol level. The recommended levels of this indicator are <1000nmol/L.

In the recent years the presence of elevated lipoprotein(a) [Lp(a)] levels has started to attract at-
tension as an important risk factor (22). Lp(a) is an LDL-like particle where apolipoprotein(a) is connected to apoprotein B-100 via a disulphide bridge. In addition to being a cholesterol carrier in the organism, Lp(a) is probably linked to atherosclerosis and inflammation processes and to platelet formation. Lp(a) is significantly linked to acute-phase inflammatory proteins and promotes the proliferation of the vascular smooth muscle cells, as well as the monocyte chemotaxis and the conversion of macrophages into foam cells. It has been proven that the presence of elevated Lp(a) levels has an independent impact of the occurrence and progress of CVDs (22,23). In the Framingham Heart Study, men with IHD had significantly higher Lp(a) levels. Although women were prone to having higher Lp(a) levels, they were not statistically significant (24).

The new indicators for LDL concentration are already included in the recommendations of the National Lipid Association in the US for atherogenic risk assessment, but they are invariably combined with the levels of the total cardiovascular (CV) risk and their assessment must be conducted only in high-risk patients and those with moderately high risk (Fig. 1) (23).

Of all cholesterol subclasses, HDL cholesterol is the most important protective factor against CVDs. Just like other TC subclasses, it is also a heterogeneous group containing several subclasses – HDL2 and HDL3 depending on the presence of different types of apolipoproteins (AI-AIV, E, C, D), lipids, enzymes and transport proteins (25). The atheroprotective effect of HDL cholesterol is due to several apolipoprotein functions:

1. participation in the reverse cholesterol transport (26) via intake of cholesterol from lipid-loaded

<table>
<thead>
<tr>
<th>CRP</th>
<th>Lp-PLA2</th>
<th>ApoB</th>
<th>LDL-P</th>
<th>Lp(a)</th>
<th>HDL or LDL subfractions</th>
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**Fig. 1.** U.S. recommendations for analyzing additional indicators of lipid metabolism and inflammatory markers (23)
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Gordon and associates calculated, in a meta-analysis of four large-scale American epidemiologic studies, that for every 1 mg/dL serum HDL cholesterol increase, the coronary risk was reduced by 2% in men and by 3% in women, regardless of the other risk factors and the LDL cholesterol level (28). It has already been established that HDL cholesterol levels are not the only factor, which plays a role in CVD protection, but also the functional fitness and size of the particles (HDL-P). In a study including patients with an increased intima/media ratio and coronary atherosclerosis, the cholesterol efflux is an independent predictor of CV incidents with a reverse correlation (29). HDL particles are also important, just like with LDL. Mackey and associates (30) found that an increase in the HDL-P number by 1 standard deviation decreased the intima/media ration by 0.022 mm (95% CI 0.011-0.034 mm) and the coronary heart disease (CHD) risk by 25% (95% CI 7-39%), whereas the effect of the HDL cholesterol level disappear after controlling the level of LDL and HLD-P. A similar association was also found in the EPIC trial where the change in HDL-P decreased the CHD risk by half (OR=0.50, 95% CI=0.37-0.66), independent of other factors (31). Of importance is also the apolipoprotein A-I concentration because it comprises 70% of the total HDL protein and the number of its molecules is different in the different HDL particle subclasses. The large spherical HDL-P carry 4-5 macrophages, also known as “cholesterol efflux capacity”. This mechanism represents an important HDL function and play a key role in CV protection;

2. participation of HDL cholesterol in the protection against oxidative stress, which includes not only protection against serum LDL cholesterol, but also against unfavorable intracellular impact of oxidized LDL;

3. anti-inflammatory effects of HDL cholesterol on the monocytes and endothelial cells;

4. anti-platelet activity due to the HDL cholesterol-mediated inhibition of the platelet activity;

5. HDL cholesterol ability to stimulate endothelial prostacyclin synthesis, thus promoting vasodilation through its ability to prolong its plasma half-life. The increased endothelial NO-synthase production is added to this;

6. the ability of high-density lipoproteins to regulate the thromboxane and prostaglandin production and activate the fibrinolytic system, thus improving platelet lysis;

7. HDL cholesterol ability to bind endotoxins and protect against their effects in vivo (25, 27).

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DYSLIPIDEMIA MANAGEMENT

The treatment of lipid metabolism disorders is determined by the LDL cholesterol levels, which are the primary target to be influenced, as well as by HDL cholesterol (34). According to the latest management recommendations in Europe, TGs are not a single therapeutic target but have to be monitored in the presence of dyslipidemia with elevated TG levels (class IIa B) (4).

Currently more attention is paid to non-fasting TGs, which are probably more strongly related to elevated risk, independent of HDL cholesterol (34). According to the latest management recommendations in Europe, TG levels are linked to the CVD risk in single-factor analyses but their effect weakens after controlling for other factors, especially HDL cholesterol. Elevated TG levels contribute indirectly to an increased atherosclerosis risk in several ways (33): by the IDL cholesterol-rich residual particles, which are formed by the large TG-rich particles under the influence of lipoprotein lipase; by altering the LDL cholesterol metabolism, which, in the presence of elevated TG levels, turns into small dense LDL particles (LDL III) under the influence of lipase and these particles have higher atherogenic capacity; by increasing the HDL cholesterol clearance through hepatic lipase since the TG-rich small HDL particles decompose faster and leave the blood circulation more easily than the large TG-depleted HDL particles. This leads to the formation of especially strongly atherogenic lipoprotein phenotype, which includes high TG levels, low HDL cholesterol and presence of elevated number of small dense LDL particles. This phenotype is characteristic of metabolic syndrome and type 2 diabetes.
### Dyslipidemias - Contemporary Understanding and Behavior

Mание се отделя на ТГ, изследвани не на гладно, които може би повече се свързват с повишен риск, независимо от HDL-холестерола (34). В последните препоръки за поведение в Европа ТГ не са самостоятелен терапевтичен таргет, но трябва да се проследяват при наличие на дислипидемия с високи нива на ТГ (клас IIaB) (4). Като вторичен таргет на лечение при комбинирана хиперлипидемия, диабет, метаболитен синдром и хронични бъбречни заболявания, чрез който вероятно се опосредства влиянието на ТГ, е неHDL-холестеролът. Проспективни проучвания показват, че комбинираният ефект на най-високите нива на неHDL-холестерола е 2.5 пъти по-голям за развитие на ССЗ (35).

### ПОВЕДЕНИЕ ПРИ ДИСЛИПИДЕМИЯ

Лечението на нарушенията в липидния метаболизъм се определя според нивата на LDL-холестерола, който е първична цел на влияние (Фиг. 2) (по 4).

Като първичен таргет се препоръчва LDL-холестеролът, тъй като доказателствата за ефективността от снижението на нивата му са най-много и най-значими (клас IA). Когато анализът му е невъзможен, като таргет за лечение се допуска и ОХ (клас IIaA). Както вече споменахме, нивото на ТГ трябва да се проследява, когато изходно е повишено (клас IIaB). Като вторични цели на лечение са съхраненицие на нивата на HDL-холестерола и LDL-холестерола, но трябва да се оценят същевременно нивата на неHDL-холестерола и ТГ. В таблици 2 представяме препоръчителната терапия за различните нива на цели, както и съответните медицински манипулации (Фиг. 2) (4).

### Assessment of the laboratory lipid indicators

<table>
<thead>
<tr>
<th>Score CVD risk</th>
<th>LDL-cholesterol levels</th>
<th>Class/Level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lipid correction</td>
<td>No lipid correction</td>
<td>I/C</td>
</tr>
<tr>
<td>Lifestyle changes</td>
<td>Lifestyle changes</td>
<td>I/C</td>
</tr>
<tr>
<td>+ consider medical therapy</td>
<td>+ consider medical therapy</td>
<td>I/C</td>
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<tr>
<td>I/C</td>
<td>I/C</td>
<td>IIa/A</td>
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<tr>
<td>Lifestyle changes, medical therapy</td>
<td>Lifestyle changes, medical therapy</td>
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Fig. 2. Management in the different patients according to the LDL cholesterol level and CV risk (4)

### Diet-related measures

- **Unsaturated fatty acids**: <7% of the total energy intake.
- **Trans unsaturated fatty acids**: Replaced with mono- and polyunsaturated fatty acids.
- **1%** of the daily energy intake, received by unsaturated fatty acids, is replaced by monounsaturated fatty acids, the LDL cholesterol level will decrease by 0.041 mmol/L, and if it is replaced by n-6 polyunsaturated ones, the reduction of the LDL cholesterol level will be by 0.051 mmol/L (36).
- **n-3 polyunsaturated fatty acids**: (>2g/daily) reduces also the TG levels. However, for this purpose food sources are not enough and nutritional supplements or medicaments are needed. In patients with severe forms of hypertriglyceridemia a significant reduction of fats in food is required (<30g/daily). They must be less than 35% from the total energy intake. In addition, a decrease of the total carbohydrate intake is needed, especially carbohydrate foods with high glycemic index/low fiber content (4).
Диетичните мерки се препоръчват за всички видове дислипидемия. Основно значение има ограничаването на насищентите мазни киселини (<7% от общия енергийен внос) и на транс-насищентите мазни киселини, като те се заменят с моно- и полиена нативи мазни киселини. Ако 1% от дневния енергийен прием, получен от насищентите мазни киселини, се замени с моноена нативи мазни киселини, LDL холестеролът ще намаляе с 0.041 mmol/l, а ако се замени с п-6 полиена нативи, то редукцията в нивото на LDL-холестерола ще е с 0.051 mmol/l (36). Използването на висока концентрация на п-3 полиена нативи (>2 г/дневно) намалява нивата и на ТГ, като за тази цел не е достатъчна само доставката от хранителни източници, а са необходими и хранителни добавки или медикаменти. При болни с тежки форми на хипертглицеридемия е необходимо и значима редукция на ненасищентите мазни киселини в храната (30 г/дневно), които да са под 35% от общия енергийен внос, и намаляване на общия въглехидратен внос, особено на въглехидрати храни с висок гликемичен индекс/ нисък състав на фибри (4). По отношение на HDL-холестерола редукцията на транс-насищентите е от най-голямо значение, докато ограничаването на насищентите и повишения количества на ненасищентите мазни киселини нямат толкова отчетлив ефект. Умереният прием на алкохол (1-2 питиета дневно, което отговаря на 10-30 г/дневно) редуцира ТГ и повишава нивата на HDL-холестерола, но по-големи количества могат да увеличат ТГ значимо. Добавянето на въглехидрати (захарни изделия не повече от 10% от общия енергийен внос), фибри, соя, фитостероли и други хранителни добавки биха подобрили липидната обмяна.

От другите мерки за промяна в начина на живот намаляването на телесното тегло с 5-10% и повишаването на ежедневната физическа активност до 30 мин/дневно повлиява благоприятно всички показатели на липидната обмяна, както и глюкоznата обмяна и инсулинова чувствителност. Спиране на тютюнопушенето повишава HDL-холестерола умерено. Ограничаването на солта под 5 г/дневно намалява стойностите на артериалното налягане и по този начин редуцира общия CC риск.

**MEDICAL THERAPY**

Statins still remain the main antilipemics. They significantly reduce TC and LDL cholesterol levels, moderately decrease the TG level and slightly increase the HDL cholesterol level. Meta-analyses show that the use of statins reduces the total mortality rate by 10%, CV mortality by 20%, the incidence of coronary incidents by 23% and that of brain stroke by 17% for every 1 mmol/L decrease of the LDL cholesterol level (37). Currently, the following algorithm for choosing a statin is suggested (4):

- assessing the individual CVD risk and including the patient in the process of decision-making in regard to influencing the CV risk;
- determining the target LDL cholesterol levels for the respective risk level;
- calculating the percentage of LDL cholesterol reduction needed to achieve the goal;
- choosing a statin, which based on literature data will ensure the needed LDL cholesterol decrease;
- since the response to statins is variable, increasing the dosage is almost compulsory;
- combined therapy is needed in case of no effect after monotherapy.

The side effects from the use of statins are few and rare. The most serious one is myopathy, which can progress to rhabdomyolysis. Fortunately, it occurs relatively rarely - <1/1000 patients treated for myopathy and <1/1000000 for rhabdomyolysis. Myalgia, without creatine kinase (CK) level elevation is ob-
MЕДИКАМЕНТОЗНА ТЕРАПИЯ

Основни антилипемични средства остават статините. Те намаляват значимо нивата на ОХЛ и на LDL-холестерола, умерено снижават ТГ и леко повишават HDL-холестерола. Мета-анализи показват, че приложението на статини намалява общата смъртност с 10%, СС смъртност – с 20%, честотата на коронарните инциденти – с 23%, и на мозъчния инсулт – със 17% за всеки 1 mmol/l снижение на LDL-холестерола (37). Понякога се предлагат следната схема на избор на статин (4):• оценка на индивидуалния риск от ССЗ и включване на индивида в процеса на вземане на решения за въздействие върху параметри-те на неговия СС риск;• установяване на таргетните стойности на LDL-X за съответното ниво на риск;• изчисляване на процента на редукция на LDL-X, необходим да се постигне целта;• избор на статин, който по данни от литератур-ата би осигурил такова снижение на LDL-X;• тъй като отговорът към действията на статините е много вариабилен, повишаването на дозите е почти задължително;• при липса на ефект от монотерапия със ста-тин за постигане на целта, да се приложи комбинирано лечение.

Страничните ефекти от приложението на стати-ните са малко и редки. Най-серозното от тях е миопатията, която може да прогресира до рабдо-миолиза. За щастие, те са сравнително ряд-ко - <1/1000 лекувани болни за миопатията и <1/1000000 за рабдо-миолизата. Милатия, без повишение на стойностите на СК, се среща при 5-10% от болните, но рядко е причина за пре-късване на лечението. Рискът от развитие на миопатия се повишава при комбиниране на статин с фибрат. Повишение на чернодробните ензими над 3 пъти горна референтна граница в два следе-дователни изследвания се наблюдава при 0.5-2% от лекуваните и е обикновено дозазависимо. Нас-коро се появиха съобщения за леко повишение на риска от захарен диабет тип 2 при прием на ста-тини, но това не бива да ни обезкуражава да при-лагаме статини при индикации за това, тъй като съотношението полза/риск за този клас медика-менти е силно положително. Като алтернатива на статините при непоносимост могат да се обсъдят жълчни киселини, инхибитори на холестеролова-та абсорбция (ezetimib) и нияцин. Комбинация-та на статин с езетимид може да намали LDL-X допълнително с 15-20% и може да се използва served in 5-10% of the patients but it is rarely a reason to interrupt the treatment. The risk of myopathy is increased when combining statins with fibrates. A 3-fold elevation of the liver enzymes in two consecutive tests is observed in 0.5-2% of the patients and is usually dose-dependent. There have recently appeared publications about a slightly increased risk of type 2 diabetes after statin intake but this need not discourage us from using statins if there are indications for it because the benefit/risk ratio of this class of medications is strongly positive. Bile acids, inhibitors of the cholesterol absorption (ezetimibe) and niacin can be considered alternatives to statins in cases of intolerance. A combination of statin and ezetimibe can additionally decrease the LDL cholesterol level by 15-20% and can be used when the therapeutic goal is not achieved.

Fibrates are antilipemics of choice in hypertriglyceri-demia when the TG levels are >2.3 mmol/L and when the CV risk is high. Despite the fact that the data about their application is controversial, they can reduce TG levels by 50% and increase HDL cholesterol levels by 10-15% in the short term and 5% in the long term. Meta-analyses show that fibrates reduce the incidence of the main CV incidents by 13% (95% CI 7-19%), especially in patients with elevated TG levels >2.3 mmol/l and low HDL cholesterol levels. The use of potent statins in high doses can decrease the TG levels by 30% along with other benefits they carry. The uses of n-3 fatty acids, nicotinic acid (not recommended currently), as well as a combination of statins and fibrates, omega-3 fatty acids, niacin, and fibrates combined with fatty acids are considered alternative therapies.

The increase of HDL cholesterol levels is not con-sidered a primary goal now because in clinical studies no correlation was found between the elevation of HDL cholesterol levels and CVD incidents. For the moment lifestyle changes are recommended, the use of statins and fibrates only partially solves the problem. The application of potent medications to treat the hypoHDL-emia is not approved for the moment due to the inability to improve the patient prognosis or due to numerous serious and frequent adverse effects. The use of nicotinic acid, alone or in combination with laropiprant is now considered un-founded after several trials (HPS-2 THRIVE, AIM-HIGH) did not confirm the positive effect on CV incidents. Another group of medications, which in-hibit the cholesteryl ester transfer protein (CETP-I), represented by torcetrapib, dalcetrapib, anacetrapib, evacetrapib, have not gained popularity for the moment due to their side effects and the lack of effi-
CETP-I), as well as dalcetrapib, anacetrapib, evacetrapib, and torcetrapib, which are inhibitors of the cholesteryl ester transfer protein (CETP). These drugs have been approved for treating patients with primary hypercholesterolemia: lomitapide, which is an inhibitor of the microsomal TG transfer protein (MTP), and mipomersen, which is an inhibitor of the antisense oligonucleotide (ASO), being mainly directed to apoB-100. Monoclonal bodies to PCSK9 have been developed as well with their action being similar to the genetic decrease of LDL cholesterol levels via blockage of this protein responsible for the disintegration of the lipoprotein receptor in the hepatocytes. Darapladib is an inhibitor of the lipoprotein associated phospholipase A2 (LpA2) enzyme, which is carried by the LDL particles and is transported into the vascular wall. It has been tested in 2 trials with an end result CV incidents. Canakinumab is a monoclonal antibody to interleuken-1β and aimed at the inflammation processes and the increase of interleuken-1β by the cholesterol crystals in the atheromatous plaque.

CONCLUSION

Dyslipidemias are a main risk factor for the occurrence of CVDs. They develop as a result of the interaction of numerous genetic changes with environmental factors. Its incidence in the general population is high, especially among CVD patients. Dyslipidemias are a group of lipid metabolism disorders and frequently include complex interactions between the separate lipid subclasses in the organism. Their modern treatment is aimed at decreasing the LDL cholesterol level as a primary target and includes both measures for lifestyle and diet changes, and medical therapy. Statins are the drug of choice in almost all dyslipidemias, being applied alone or in combinations, whereas fibrates and other antilipemic medications have a limited use. In order to reduce the residual CV risk, new solutions, beyond the decrease of the LDL cholesterol levels with statins, are sought.

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гонуклеотид (ASO), като основно е насочен към apoB-100. Разработени са и моноклонални антитела към PCSK9, чието действие е да наподоби генетично детерминирано снижение на нивата на LDL-X посредством блокиране на този протеин, отговорен за разграждането на липопротеиновия рецептор в хепатоцитите. Darapladib е инхибитор на ензима липопротеин-свързана фосфолипаза A2 (LaP A2), който се носи от LDL-частиците и се пренася в съдовата стена, и е тестван в 2 проучвания с краен изход СС инциденти. Canakinumab представлява моноклонално антитяло към interleuken-1β и е насочено към процесите на възпалението и увеличението на interleuken-1β от холестероловите кристали в атероматозната плака.

ЗАКЛЮЧЕНИЕ
Дислипидемиите са основен рисков фактор за развитие на ССЗ. Те се развиват в резултат на взаимодействие на множествени генетични промени с фактори на околната среда. Честотата им е висока в обществата популяция и особено сред пациентите със ССЗ. Дислипидемиите са семейство нарушения в липидния метаболизъм и често включват сложни взаимоотношения между отделните подкласове липиди в организма. Съвременното им лечение е насочено към намаляване на LDL-холестерола като първична цел и включва както мерки за промяна в начина на живот и храненето, така и медикаментозно въздействие. Средство на първи избор при почти всички дислипидемии са статините, самостоятелно или в комбинации, докато фибратите и други антилипемични медикаменти са с ограничен принос. За да се намалят остатъчният СС риск, се търсят нови решения отвъд намаляването на LDL-холестерола със статин.

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