



## Review Article

# Some aspects of Treatment of Patients having Dislipidemia on the Background of Hypertension

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### Abstract

At present dislipidemia and hypertension are considered as leading independent risk factors of cardio-vascular pathology. Their effective treatment leads to significant decrease of occurrence of cardio-vascular diseases and mortality because of these reasons. There is an opinion among physicians that the capabilities of non-medication impact on treatment of dislipidemia on the background of hypertension are rather underestimated. We mean rational diet and dosed exercises, especially on the background of continuous intake of medicines.

The aim of the study is to state the results of modern investigations concerning treatment of dislipidemia and hypertension combination.

It is confirmed in the literature is that effective lowering of arterial pressure level and removal of dislipidemia are the basis of treatment and prophylaxis of atherosclerosis? Besides, the achievement of purposeful values of given indices is possible far not always. In this connection it is necessary to heighten attention to simultaneous conducting of hypolipidemic and hypotensive therapy. It is possible for most patients with different level of cardio-vascular risk. There were stated the aspects of complex treatment of dislipidemia and hypertension with taking into consideration the level of cardio-vascular risk. There were considered in detail the last ideas about pathogenic connections between dislipidemia and hypertension. It was shown the role of hypercholesterolemia as a factor lowering bioavailability of nitric oxide, rising rigidity of a vessel wall, increasing sensibility of smooth myocytes to natrium and strengthening the functioning of calcium channels. At the same time, high arterial pressure increases the speed of atherogenic lipoproteins' penetration into a vessel wall with the help of pressure convection, during which parts of lipoproteins enter the structures of subendothelium. There was summarized the information received from different clinical investigations concerning estimation of therapeutic capabilities of combined application of statins and hypotension medicines to patients with dislipidemia and hypertension. There were cited the data about the results of usage of fixed combinations of preparations from these groups with taking into consideration the attachment degree of patients to prolonged therapy.

### Keywords

Hypertension; Alimentary dyslipidemia; Combined therapy; Statins; Hypotensive treatment; Attachment to therapy

### Introduction

At present dislipidemia and hypertension (AH) are considered as leading independent risk factors of cardio-vascular pathology. The effective treatment leads to significant decrease of occurrence of cardio-vascular diseases (CVD) and mortality because of these reasons [1]. At the same time, physicians often have difficulties in selecting individual treatment and establishing priorities in prescribing hypolipidemic or hypotensive therapy. They also have difficulties in making decision about the moment of joining of medication to non-medication impact as both of them aim at treatment of existing in body dysfunctions [2].

Such questions are most often considered at the debut of treatment when the necessity of immediate prescription of pharmacological preparations seems to be open for discussion. At the same time, it is noted that there exists some underestimation of capabilities of non-medication treatment – rational diet and dosed exercises, especially during continuous intake of preparations. To minimize these difficulties it is necessary to estimate attentively the state of cardio-vascular system in the result of application of instrumental and laboratory diagnostic approaches, rise of patients' attachment to therapy, reasonable combination of medication and non-medication with taking into consideration modern recommendations concerning diagnostics and treatment of cardio-vascular system pathology [3].

The aim of the present article is to state the results of modern investigations concerning treatment of dislipidemia and hypertension combination.

Points of view on the levels of cardio-vascular risk (CVR) in European recommendations ESC and EAS concerning diagnostics and correction, including alimentary dislipidemia, were exposed to serious revision in comparison with their previous variants. It is traced brightly in recommendations worked out by Russian National Society on the investigations of atherosclerosis of 2012. Introduced changes touched not only tables of CVR ascertainment according to scale SCORE (Systematic Coronary Risk Evaluation), but also descriptions of patients' categories with different risk. Both Russian and European recommendations contain the following data.

IDH very high risk is common for patients with ischemic heart disease and/or symptoms of atherosclerosis of peripheral arteries, old ischemic stroke, confirmed by methods of investigation (radiological investigation, stress-echo-cardiography, coronarography, duplex scanning of arteries); people having diabetes (DB) of the 1<sup>st</sup> and 2<sup>nd</sup> types and affections of organs-targets (microalbuminuria); patients with chronic renal insufficiency, 10 years' risk according the scale SCORE 10% and more.

High risk: presence of just one evident risk factor including genetically or alimentarily conditioned dislipidemia (or concentration of common cholesterol –CCS – more than 8.0mmol/l) , or evident AH, 10 years' risk of death from CVD according to the scale SCORE 5% and more but lower than 10%.

Moderate risk: 10-years' risk according to the scale SCORE 1% and higher but lower than 5%. This group is mostly composed of middle-aged persons. In succeeding years risk revision is conducted taking

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into consideration family anamnesis of CVD (men – younger than 55 years and women – younger than 65 years), obesity presence of abdominal type, level of physical activity, concentration of cholesterol (CS) of high density lipoproteins (LPHD), triglycerides (TG), quantity of C-reactive protein, fibrinogen, LP (a), apoprotein B, homocystein and social position.

Low risk: 10-years' risk according to the scale SCORE lower than 1%.

The most important change took place in a new point of view on an idea of high and very high risk. Now, being based on last recommendations, we speak about the presence of very high CVR when there are not only acute but also chronic symptoms of coronary atherosclerosis. In this case patients with evident hypertension without any other risk factors are considered to have high risk what dictates achievement of purposeful level of CS of lipoproteins of low density (LPLD) – lower than 2.5mmol/l. The scale SCORE is used at finding out of all the risk categories. But there are some limitations: finding out the risk with the help of the given scale shouldn't be conducted in case of patients having proved CVD, i.e. at presence in their anamnesis of myocardial infarction or acute abnormality of brain circulation at proved DB of any type, with microalbuminuria, heavy AH, hereditary hyperlipidemia, and chronic renal failure. These patients are automatically considered as having very high and high risk of cardio-vascular abnormalities and need carrying out of intensive impact aimed at removal of risk factors. There are some additions to the application of the scale SCORE in the last version. So, given scale gives possibility to estimate the risk of appearance of not only fatal events but for nearest 10 years. With this aim we should multiply found on the scale SCORE risk (fatal CVD during 10 years) by 4 in case of women and by 3 in case of men. Besides, presence of additional risk factors rises the common CVR (including low concentration of CS of LPHD). Even in case of low and moderate risk (lower than 5.0% according to the scale SCORE) the level of systolic arterial pressure (AP) needs correction by medication. The connection between the value of CVR and purposeful concentration of CS of LPLD isn't revised. At the same time, taking into consideration the removal of chronic forms of ischemic heart disease (IDH) from the zone of high risk into the zone of very high risk, we can speak about widening of the region of initial prophylaxis of clinical symptoms of heart vessels' atherosclerosis. Patients having AH and moderate dislipidemia form a separate group.

It is known that AH and dislipidemia contributed the process of atherogenesis from the point of view of independent CVR factors [4,5]. At the same time, great attention should be devoted to their simultaneous presence with synergizing interaction [6-8]. In experimental works they showed the role of hypercholesterolemia as the factor lowering bioavailability of nitric oxide (NO), rising rigidity of vessels' wall, increasing sensibility of smooth myocytes to sodium and strengthening the functioning of calcium channels [9,10]. It was established that elasticity of vessels' wall in zones, which are near to developing atherosclerotic plague, experience evident changes, including signs of short-period hyperelasticity and its notable decrease [11,12]. Mechanical characteristics of large and middle vessels of patients with primary dislipidemia begin to change long before the appearance of AH symptoms. In case of family hypercholesterolemia the beginning of vessels' remodelling can be found already in childhood [13]. Spring characteristics of a vascular wall are also broken in presence of secondary dislipidemia, i.e. of diabetic, nephrogenic, postmenopausal origin [14-16]. Among many factors influencing

indirectly mechanical peculiarities of vessels there is low level of CS LPHD and hypertriglyceridemia [17]. Given factors promote stable AP rise. It was found that durably existing hypercholesterolemia is closely connected with macro vascular abnormalities. CS rise in arterioles leads to significant damage of structure and functioning of micro vascular system on the whole and to strengthening of platelets' aggregation. It is accompanied by density decrease of microvascular bed. It can be watched in different organs including kidneys, muscular tissue and fatty tissue. It leads to the rise of peripheric resistance what promotes the rise of AP level. It becomes clear that notwithstanding the absence of the direct morphological atherosclerosis symptom, i.e. atherosclerotic plague, in vessels of microcirculatory course, durably existing hyperlipidemia damages significantly circulation in these vessels [18]. Besides, rise of aggregative features in platelets is noted with aging even without evident dislipidemia what worsens microcirculation [19]. Last years' works allowed also finding feedback of AH with the flow of atherosclerotic damage of vessels. In our experiment we showed direct impact of high AP on penetration degree and speed of atherogenic lipoproteins into a vessel's wall. It was supposed that there are some variants of the given events. Among them we see pressure convection during which supramolecular complexes, i.e. parts of lipoproteins, under the impact of pressure penetrate into sub endothelium structures. As one more rather possible mechanism we see strengthened transfer of LP into vessels' walls because of their mechanical sprain on the background of high AP. In conditions of experiment it was noted that parts of lipoproteins can accumulate near inner elastic membrane of a vessel what is dangerous as far as development and progressing of atherosclerotic plague are concerned [20]. Endothelium state is very important for pressure convection of lipids into a vessel wall. In conditions of AH mechanical barrier function of endothelium weakens leading to increase of lipoproteins' inflow into intima and media of vessels what is especially brightly seen at presence of hyperlipidemia [21]. Mathematical calculation was made on the basis of understanding of a vessel wall's multilayerness and taking into consideration shift speed. With the help of it it was found that AH provides migration of lipids into a vessel wall at lowering of shift speed near atherosclerotic plaques [22].

The investigation of ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) turned out to be many-centered clinical investigation during which there were confirmed some ideas about interaction of hypotensive and hypolipidemic therapies [23]. During this investigation patients, who received amlodipin or athenolol and had the level of CCS less than 6.5mmol/l and didn't receive statins or fibrates (on the whole 10, 305patients), got 10mg of athorvastatin or placebo. In our treatment we also added perindopril to amlodipin and bendroflumethiazide-potassium to athenolol with the aim of achievement of purposeful AP meanings. In our investigation athorvastatin lowered significantly the number of new cases of infarctions and strokes among persons with well controlled AH at absence of IDH. At comparison of results with placebo it became clear that intake of athorvastatin provided risk decrease on 37% of nonfatal cardiac infarction and a case of fatal IDH during investigation and was associated with lowering of CCS and CS of LPLD on 1.1 and 1.0 mmol/l, correspondingly. Received data were compared with other hypolipidemic investigations and provided understanding of aspects of primary IDH prophylaxis among persons with AH in case of effective AP control on the background of moderate CVR. It was found out that patients who received amlodipin had much less cardio-vascular episodes (i.e. infarctions, strokes and sudden cardio-vascular deaths), than persons who received athenolol. We didn't get significant

differences between groups with amlodipin and athenolol in the field of lowering of TG, CCS and CS of LPLD in case of athorvastatin addition. CS level of LPHD rose also independently from prescribed hypotensive preparation.

Many-centered investigation GEMINI evaluated application of amlodipin and athorvastatin in 1pill during 14 weeks [24,25]. During this investigation there were examined 1,220 patients with AH and dislipidemia. They were tried to lead out on purposeful levels of CS LPLD and AP. Purposeful AP level was noted in 65%, and purposeful values of CS LPLD – in 82% examined persons what turned out to be the most optimal in the plan of achievement of given therapeutic aims in comparison with other investigations. Besides, in given investigation we confirmed good tolerance of immediate application of athorvastatin and amlodipin. It was also said in the investigation AVALON [26] when more than 45% patients who received fixed dose of amlodipin/athorvastatin reached purposeful levels of AP and CS LPLD, recommended by the 7<sup>th</sup> United National Committee JNC7 and National Educational Programme on cholesterol.

In additional investigation AVALON-AWC they worked out the hypothesis about the impact of athorvastatin and amlodipin combination on endothelium state and indices of arterial wall's elasticity. It was found that maximum positive effect of treatment, as far as spring characteristics of vessels and endothelium functions are concerned, is possible at combination of amlodipin and athorvastatin [27].

In the investigation RESPOND there was also shown the prospectivity of combined application of athorvastatin and amlodipin which allowed lowering AP on 12.8-17.5mm merc. col., and concentration of CS LPLD – on 37-48% [28].

The investigation JEWEL, consisting of two parallel investigations JEWEL I and JEWEL II, was also of great practical interest. The first one of them was conducted in Canada and Great Britain, where they have their own recommendations differing from those of the European Society of Cardiologists, and the second investigation (JEWEL II) – in some European countries. The investigation lasted for 16 weeks. More than 2,200 patients took part in it. They were given 5mg of amlodipin and 10mg of athorvastatin with the increase of amlodipin dose to 10mg in case of necessity. To the end of investigation approximately 55% of patients reached the purposeful level of AP and CS LPLD at any amlodipin doses. Most patients reached the purposeful level of accountable indices [29,30].

The data centred investigation called CRUCIAL is also of great interest. Russian researchers took part in it too [31,32]. There were examined about 1,500 patients of 35-79 years with AH, concentration of CCS in blood lower than 6.5 mmol/l, with 3 and more CVR factors, at IDH absence in anamnesis. It was found that at addition of athorvastatin/amlodipin combination to «usual» therapy, the patients had evident lowering of calculated CVR. Besides, received results of data analysis with the application of European scale of fatal CVR SCORE coincided with data, received at application of Framingham scale.

The results of conducted investigation CRUCIAL confirmed previous investigations in the field of hypolipidemic and hypotensive effect. Notwithstanding the fact that determining of risk is considered to be surrogate endpoint and shouldn't be connected with real lowering of cardio-vascular catastrophes' occurrence, found information is undoubtedly important not only for clarifying of efficiency

of estimated therapy but also for estimation of signification of application of risk level calculation in case of strategy of therapy. Now there are a great abundance of investigations about positive impact of statins' addition to amlodipin and other hypotensive preparations [33-36]. However, profound study of safety and efficiency took place only in the field of fixed combinations of amlodipin and athorvastatin. Given investigations allow to consider that patient's intentions to keep prescriptions have great significance for the achievement of purposeful values at correction of risk factors. Application of fixed combinations of preparations also promotes it.

At proper time begun correction of AH and abnormalities of lipidic metabolism is necessary for efficient therapy [37]. At the same time, the need to take in some preparations at once influences the attachment of patients to therapy and its stable maintenance. There are some objective variants of given characteristics' estimation which depend on a number of factors. Attachment's degree to therapy can be clarified by different ways: simple questionnaires, analysis of prescriptions or determining of untaken pills, and also – direct estimation of the remedy quantity in blood or usage of containers with chips determining the time and number of doses of prescribed remedies [38]. Attachment to therapy depends not only on the number and group of prescribed medicines but also on sex, age, accompanying diseases, stage of treatment and its efficiency [39]. The connection between attachment to therapy and its efficiency is clarified on the basis of results of instrumental and laboratory examination, and also taking into consideration the levels of morbidity and mortality. It was found out in some investigations that patients are without adequate treatment for nearly 30% of time in a year because of weak attachment to it [40]. In most investigations of patients with AH and dislipidemia it was established that strong attachment to therapy leads to reliable positive results in the plan of surrogate end points and level of morbidity, quantity of hospitalizations and number of fatal cases [41]. Interconnection between strictness of treatment fulfilment and end points are often watched in results of many-centered investigations in the field of efficiency and safety of remedies where strict following the prescriptions is an obligatory condition of their conducting. In real situation nearly 1/3 of patients don't fulfil recommendations to the full extent what is necessary for purity of investigations [42].

The number of prescribed medicines significantly influences observation of terms and succession of remedies' intake. Made meta-analysis of 29 different investigations of patients with CVD at conducting of electronic monitoring of fulfilled therapy showed that increase of pills' quantity leads to significant lowering of attachment to therapy, and is connected with the number of prescribed preparations. The researchers came to this conclusion after the examination of patients with AH and dislipidemia and IDH who received medicines from 1 time a day to 4 times a day. At that, attachment to therapy lowered in comparison with single therapy on 26.7%, 39,0% and 54.2% in case of twofold, threefold and fourfold intakes of pills, correspondingly [43]. At the same time, though the switch to combination of two preparations in 1 pill has many advantages, it's difficult to realize it in conditions of a clinic because of its higher cost and limited quantity of combinations of prescribed doses what leads to difficulties in selecting the necessary treatment [44]. It will be right to say that attachment to therapy with application of only two definite combinations, registered in Europe, was compared with analogical one in the USA [45]. DUPLECOR is registered now both in Europe and in Russia. It contains amlodipin and athorvastatin in doses 5/10, 5/20, 10/10 and 10/20 what turned out to be a good argument for

application of nondivisible pills with stable combination of given medicines, positively influencing the components of haemostasis system and weakening thrombosis risk [46].

## Conclusion

Efficient lowering of AP level and removal of dislipidemia are general strategy and prophylaxis of atherosclerosis. This directive is in different international and Russian recommendations. At the same time, achievement of purposeful values of given indices is possible far not often. In this connection it is necessary to devote more attention to simultaneous conducting of hypolipidemic and hypotensive therapy. That is why, it can be considered natural that fixed combinations of a hypotensive preparation and a statin are more and more often prescribed to patients. Fixed combination of atorvastatin and amlodipin is rather wide-spread in Europe. It becomes clear that prescriptions of such medicines are possible to most patients with different CVR level.

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