

Combinator Individual Lipid-Lowering Therapy-What Is The Right Direction?

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Abstract

Dyslipidemia is one of the most important risk factor for cardiovascular diseases, which are the main cause of death worldwide. There are two treatment options for dyslipidemia that complement each other. Despite the spread of lipid-lowering therapy and its increasing use in clinical practice, a large numbers of patients still remain in high "residual cardiovascular risk." Currently at the forefront of lipid-lowering agents, statins significantly lower LDL-cholesterol but in the terms of effect on the levels of triglycerides and HDL-cholesterol there is much less impact. This is a serious problem, especially in patients with atherogenic dyslipidemia, typical for patients with metabolic syndrome. For this reason, high attention has recently been given to combination of lipid-lowering agents. It is also important to mention the important pleiotropic effects of hypolipidemics. This article provides an overview of current lipid-lowering agents, their comparisons as well as new recommendations in the management of dyslipidemia.

Keywords: Dyslipidemia; Single hypolipidemic therapy; Combination hypolipidemic therapy

Introduction

Cardiovascular diseases are the main cause of death worldwide. Metabolic syndrome with its components is one of the most important risk factors of cardiovascular disease. The principal consequence of the syndrome components and the cause of death is atherosclerosis. Treatment of each component of the metabolic syndrome delays the development of cardiovascular complications. It is very important to provide prevention and treatment of those risk factors, to achieve the reduction of cardiovascular morbidity and mortality [1].

The therapeutic target for dyslipidemia treatment is LDL-cholesterol, which is significantly reduced by statin therapy [2]. Despite the high effectiveness of statins the death rate for cardiovascular diseases is about three quarters of high-risk patients. A serious clinical problem is the increased total cardiovascular risk, principally so-called atherogenic dyslipidemia (elevated triglycerides, low HDL-Cholesterol and elevation of small dense LDL particles, which are the most atherogenic). In patients with residual risk a combination therapy with statins and fibrates should be used.

Statins

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. They are the most efficient agents for reduction of plasma cholesterol, being also appreciated for their good tolerance [1]. The reduction in intracellular cholesterol concentration induces a low-density lipoprotein receptor (LDL-R) expression on the hepatocyte cell surface, which results in increased extraction of low-density lipoprotein cholesterol (LDL-C) from blood and decrease in concentration of circulating LDL-C and other apoB-containing lipoproteins including TG-rich particles. Statins also reduce triglyceride levels (7-30%) and increase high-density lipoprotein cholesterol (HDL-C) levels (5-15%). Lowering LDL cholesterol with statin regimens reduces the risk of myocardial infarction, ischaemic stroke, and the need for coronary revascularisation. A number of large-scale clinical trials have demonstrated that statins bring substantial reduction of cardiovascular (CV) morbidity and mortality in both primary and secondary prevention. The clinical conditions of the subjects, concomitant treatments, and drug tolerability will play a major role in

determining the final choice of drug and dose [2]. Currently, atorvastatin and rosuvastatin, have the strongest evidence and also the strongest lipid-lowering effects (maximum doses of both 80 mg and 40 mg are associated with 50-60% reduction in LDL-cholesterol). However, a substantial proportion of patients (up to approximately 50%) do not achieve LDL-C goals with statin monotherapy, particularly the patients with metabolic syndrome. High residual cardiovascular risk, however, is not an argument against statin treatment, but the reason for further intervention aimed at the reduction [3].

Statins also have significant non-lipid lowering effects. The most important antiatherogenic pleiotropic effects of statins include improvement of endothelial function, antioxidant properties, anti-inflammatory, anti-proliferative, anti-thrombotic, neoangiogenic and uricosuric effects [4,5].

Statins modulate series of processes leading to reduction of the accumulation of esterified cholesterol into macrophages, increase of endothelial NO synthetase, reduction of the inflammatory process, increased stability of the atherosclerotic plaques, restoration of platelets activity and of the coagulation process. In addition, statins can inhibit tumor cell growth and enhance intracellular calcium mobilization [6].

Statins are generally well tolerated. The most common possible adverse effects during treatment with statins are the asymptomatic elevation of liver enzymes and myopathy. Elevations of transaminases, alanine aminotransferase (ALT), aspartate aminotransferase (AST) is often asymptomatic and statin therapy should be discontinued at levels exceeding three times the upper limit of normal (sometimes even at lower increases in these enzymes). Myopathy associated with statin

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therapy represents a wide variety of conditions, ranging from myalgia (muscle pain without elevation of creatine kinase), myositis (also present elevation of creatine kinase) and ending with rhabdomyolysis (creatinine levels increased significantly, often more than ten times over the upper limit of normal also associated with an increase in creatinine). In large clinical trials, the occurrence of severe myopathy was described in 0.1-0.5% of subjects, while the incidence of rhabdomyolysis was 0.02 to 0.04%. Mechanisms of myopathy during treatment with statins are not yet fully understood. It is assumed; however, that inhibition of mevalonate has decreased the synthesis of other substances which are dependent on the formation. The most important of these are coenzyme Q10 and some selenoproteins. The risk of myopathy is increased in kidney and liver disease, diabetes, hypothyroidism, immobilization, post-operative conditions, excessive alcohol consumption but also the extreme physical exertion. It is more common in elderly and occurs more frequently in women [7,8]. Creatine phosphokinase (CK) is usually elevated and this may often be due to physiological reasons (e.g. in increased physical activity). Therefore it is necessary to approach the eventual discontinuation of therapy judiciously, after careful assessment of history (it is often necessary to re-establish the values CK), and considering the potential risks and benefits [9].

Fibrates

Fibrates have been in clinical use for over 30 years. Fibrates are ligands of peroxisome proliferator-activated receptor α (PPAR α). Fibrates are used as lipid-lowering drugs to prevent cardiovascular pathology. Besides altering lipid metabolism, PPAR α ligands exert anti-inflammatory effects on various cell types. Fibrates are well known for their beneficial effects on triglycerides (TG) (by lowering TG levels up to 50%), high-density lipoprotein cholesterol (HDL-C) (by rising up to 10-15%), and low-density lipoprotein (LDL) subclass distribution. Fibrates may also reduce LDL-C by up to 15-20% [2]. In recent years, significant progress has been made in understanding fibrate action mode. These data have shown that fibrates activate specific transcription factors belonging to the nuclear hormone receptor superfamily, termed peroxisome proliferator-activated receptors (PPAR). Activation of these receptors alters the transcription rate of target genes which play a key role in the development of atherosclerosis. Recent data from the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) analyses from the Bezafibrate Infarction Prevention trial (BIP) have demonstrated that fibrate therapy improves both insulin sensitivity and the blood lipid profile, and significantly attenuates the risk of long-term major cardiovascular events [10]. One of the most used fibrates, fenofibrate (currently the only fibrate is approved by the FDA for combination therapy with statins), has also shown to improve many other atherosclerosis-related variables, such as high sensitivity C-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (LpPLA2), apolipoprotein C-III (apoC-III), and reverse HDL-cholesterol transport there is in particular the rise of the most protective particles, thus the treatment will not only increase the level of HDL-cholesterol but also changes its quality by increasing especially large HDL particles, which are the opposite of small dense LDL particles that are the most protective in protection against atherosclerosis. PPAR α activation also increases ApoAI and ApoAII synthesis (the major proteins in HDL). Fenofibrate promotes the β -oxidation of fatty acids, thus reducing the availability of free fatty acids for triglyceride synthesis. Cholesteryl ester transfer protein (CETP) activity was found to be reduced by fibrate therapy [2,11]. In practice, fenofibrate is available in various forms and the most proper form is the nano-form

which accelerates resorption of the gastrointestinal tract (GIT), thereby increasing their bioavailability.

Fibrates were shown to exert pleiotropic effect in the artery wall. PPAR α is involved in the control of the anti-inflammatory response, via inhibition of the transcription factor NF κ B, and to attenuate the production of pro-inflammatory stimuli such as interleukin 6 and various prostaglandins, as well as the acute phase proteins, including fibrinogen and C-reactive protein. Fibrates have favorable effects on coagulation and fibrinolysis. Bezafibrate was shown to reduce levels of fibrinogen by up to 20% and fenofibrate have been shown to increase fibrinolysis and attenuate platelet hyperaggregability in hypercholesterolemic subjects [12].

Results from recent major clinical trials have shown that fibrates produce beneficial effects on atherogenic lipoproteins through activation of PPAR α , and confer long-term cardiovascular protection, both in the primary and secondary-prevention setting. Therefore, this mode of lipid-lowering therapy should be considered part of an optimal management plan in a significant proportion of patients with a high-risk metabolic profile [10].

Recently, "memory" or legacy effect" observed in patients who had previously participated in Helsinki Heart Study (HHS) and Bezafibrate study Infarction Prevention (BIP) has been reported and been treated with a fibrate (gemfibrozil). Even over 18 years later after the study treatment, the prognosis of these patients is better than in those treated with placebo, which is attributed to the possible influence of certain genes affecting lipid metabolism [13].

Ezetimibe

Low-density lipoprotein (LDL) cholesterol-lowering therapy is an important aspect for the prevention of cardiovascular disease. Ezetimibe, a selective inhibitor of cholesterol absorption from the small intestine, inhibits cholesterol absorption from the intestine by blocking the action of the cholesterol transporter, Niemann-Pick C1-Like 1 (NPC1L1) protein [14]. Ezetimibe targets uptake at the jejunal enterocyte brush border. Ezetimibe is an effective LDL-C lowering agent and is safe and well tolerated. Ezetimibe at a dosing of 10 mg/kg per day inhibited cholesterol intestinal absorption by greater than 90%, with significantly reduced levels of chylomicron and VLDL by 87% [15]. Ezetimibe is indicated in the treatment of disorders of elevated cholesterol levels, including LDL-C and ApoB, as monotherapy or in combination with statins. Combination therapy trials using ezetimibe plus statin have shown greater efficacy in terms of LDL-C reduction and anti-inflammatory effects than monotherapy with ezetimibe or statin alone. Ezetimibe is also used as an alternative option in patients who are intolerant of statin therapy. The effectiveness of ezetimibe in lowering cholesterol has been tested in various dyslipidemic populations, including familial hypercholesterolemia (FH). FH is an autosomal dominant hereditary disorder caused predominantly by mutations in the LDL-receptor gene resulting in less functional hepatic LDL receptors and subsequent decreased uptake of LDL-C from the blood. FH subjects are often characterized by severely elevated LDL-C, dermatologic findings with xanthomas, and early onset atherosclerotic vascular disease. While statin therapy is the recommended initial treatment of choice along with lifestyle intervention, many FH subjects are frequently unable to reach LDL-C goals even on high-dose statin. The additive effect of the addition of ezetimibe to statin therapy therefore makes ezetimibe an attractive add-on option for undertreated FH subjects. Ezetimibe can effectively lower sterol levels in subjects with sitosterolemia by inhibiting intestinal plant sterol

absorption. Sitosterolemia is a rare, autosomal recessively inherited sterol storage disease that results from mutations in either ABCG5 or G8 proteins, in which markedly increased tissue and plasma plant sterol concentrations can lead to premature atherosclerosis and early cardiovascular death. The clinical consequences of tissue plant sterol accumulation include premature atherosclerosis and coronary heart disease at a young age, tendon xanthomas similar to those observed in patients with homozygous familial hypercholesterolemia, hematologic sequelae including chronic hemolytic anemia and thrombocytopenia, and abnormal liver function tests. Given the inability of statins to reduce plant sterol levels and the incomplete lowering of sterol levels with other treatments such as low-sterol diets and bile-acid binding resins, ezetimibe has emerged as an effective alternative strategy. In hypercholesterolemic subjects without a diagnosis of sitosterolemia, ezetimibe therapy for 2 weeks was shown to lower sitosterol and campesterol levels by 41% and 48%, respectively. In one small multicenter study, 37 subjects with sitosterolemia were randomized to placebo or ezetimibe 10 mg daily. After 8 weeks of therapy, sterol levels were reduced by 21% in the ezetimibe group and increased by 4% in the placebo group. The reduction in sterols with ezetimibe was seen despite subjects concurrently taking bile-acid binders or statins [16,17]. Ezetimibe is a safe and well-tolerated treatment without clinically important drug interactions.

Bile acid sequestrants

Their principal mechanism of action is the building of bile acids within the intestinal lumen thereby reducing the reabsorption of bile acids and available intrahepatic cholesterol. Partial diversion of the enterohepatic circulation using bile acid sequestrants depletes the endogenous bile acid pool by approximately 40%, thus stimulating an increase in bile acid synthesis from cholesterol, which lowers low-density lipoprotein cholesterol by 15 to 26%. The mechanism by which HDL is raised is through increased intestinal production of apoA-I. The largest trial to study a bile acid sequestant as monotherapy for hypercholesterolemia was the Lipid Research Clinics Coronary Primary Prevention Trial. The most popular bile acid sequestant is colestevlam. Colestevlam has been studied in combination with statins, niacin, fibrates, and ezetimibe (including some three-drug combinations). An additive reduction in LDL-C was seen with all combinations. Other observed effects of colestevlam in combination with other lipid-lowering drugs include reductions in apolipoprotein (apo) B (with statins, fibrates, ezetimibe, statin plus niacin, or statin plus ezetimibe) and high-sensitivity C-reactive protein (with statins), and increases in apo A-I (with statins, ezetimibe, or statins plus niacin). The use of bile acid sequestrants is limited by patient adherence as these drugs commonly cause gastrointestinal side effects, especially constipation, and require large and frequent dosing. The effect on HDL elevation is usually negligible. Lastly, for the dyslipidemic patient who concomitantly has high triglycerides, these drugs have no beneficial effect [18,19].

Omega-3 Fatty Acids

Long-chain polyunsaturated fatty acids with the first double bond at the third position from the methyl terminal (so called n-3 FAs or omega-3 FAs) can be found in plants and fish. This FA is a precursor also for arachidonic acid, which is further metabolised giving rise to eicosanoids with multiple biological functions in the organism. Alpha-linolenic acid (ALA) is a substrate for elongation and thus eicosapentaenoic (EPA) and docosahexaenoic (DHA) omega-3 FAs are being produced [20]. Both EPA and DHA play

a role in modification of lipid and lipoprotein metabolism. They lower triglycerides by approximately 25 to 35% and the benefit seems to be dose dependent, being ~ 45% in subjects with baseline TG values >5.6 mmol/L (496 mg/dL) [2]. Only DHA increases HDL cholesterol shifting the distribution of HDL subclasses towards larger HDL2 particles that are more active in reverse cholesterol transport. Although, there is usually no significant change in LDL-C concentration associated with omega-3 FAs administration, DHA changes the distribution of LDL particle subfractions in favour of less atherogenic, large, buoyant LDLs. On contrary, especially with high doses of omega-3 FAs used in the treatment of hypertriglyceridemia, LDL levels may rise by 10% this effect being even more pronounced in patients with extreme TG elevations at baseline [21]. The effects on plasma lipids start to occur at daily doses of EPA and DHA of 2 to 4 grams. Very importantly, omega-3 FAs have synergistic and additive effects on plasma lipids when co-administered with statins [22]. Numerous experimental studies have shown positive effects of omega-3 FAs on coagulation and platelet function, endothelial function, arterial stiffness, inflammation etc. Most importantly, there are a few prospective clinical endpoint trials (DART, JELIS, GISSI Prevenzione and GISSI-HF) that have examined the impact of omega-3 FAs supplementation on cardiovascular outcomes in different patient populations.

Nicotinic acid

Niacin (nicotinic acid) has been used for decades as a lipid-lowering drug. Niacin, along with fibrates, is the only approved drugs which elevate HDL-C along with its effects on LDL-C and triglycerides. The results of recent trials reject the hypothesis that simply raising HDL-C is cardioprotective. However, in the case of the clinical trials, structural limitations of trial design complicate their interpretation. HPS2-THRIVE is a well-designed and powered clinical trial that has provided a definitive answer as to the efficacy/adverse response profile of a combination of niacin with a D-type prostanoid 1 (DP1) antagonist. However, it is impossible to parse with confidence the differential impact of the two elements of this combination. At face value, the results of this study and AIM-HIGH are concordant with HPS2-THRIVE and fail to support the hypothesis that raising HDLc by niacin would confer any cardiovascular benefit. However, the increment in HDLc was very modest in AIM-HIGH, which was relatively underpowered by comparison with HPS2-THRIVE; it also included niacin in the control group, albeit at a lower dose, and it was prematurely concluded. Adding to this impression, and perhaps more persuasive with respect to HDLc, is the study of human genetics, where variants associated with rising levels of HDLc are not related inversely to cardiovascular risk [23].

New hypolipidemics

ACAT-1 inhibitor

Acyl CoA: Cholesterol O-Acyl transferases (ACAT) are a small family of enzymes that catalyze cholesterol esterification and cholesterol absorption in intestinal mucosal cells and maintain the cholesterol homeostasis in the blood. Results from the study at ACTVATE phase IIb clinical trial, which took place in a double blind conditions were unpleasantly disappointing as in patients with coronary atherosclerosis pactimib could alter the progression of atherosclerosis in the coronary and other arteries. Although the development of this group continues, much of cardiologists are rather skeptical when evaluating groups ACAT inhibitors [24].

CETP- inhibitor

The cholesteryl ester transfer protein (CETP) plays an important role in the reverse cholesterol transport pathway which is involved in the redistribution of the lipoprotein particle size and composition. CETP may contribute to both HDL atheroprotective mechanisms. The goal of CETP inhibition is to increase plasma-HDL cholesterol and thereby reduce CVD risk. Interestingly, reduced CVD risk has been observed less than consistently among patients with naturally occurring CETP mutations, providing a clue that reduced CETP activity is not automatically favorable. However, CETP also transfers lipids between HDL subspecies, which remodels HDL and raises levels of certain subspecies, including HDL2 and a smaller pre- β -HDL from HDL3. Torcetrapib was the first CETP inhibitor to progress to Phase III clinical trials. Unfortunately, the mood abruptly changed, when a pivotal large-scale clinical trial, namely Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) was prematurely discontinued after torcetrapib was associated with an increased risk of CVD events and death. Furthermore, other types of CETP inhibitors are under development. The effects of anacetrapib and evacetrapib on the progression of atherosclerosis or CVD endpoints are unknown but both profoundly increase HDL cholesterol, compared to dalcetrapib. Perhaps as important, anacetrapib and evacetrapib also reduce LDL cholesterol by 35-40% [25].

Azetidinons-darapladib

Darapladib produced sustained inhibition of plasma Lp-PLA2 activity in patients receiving intensive statin therapy. The results of studies with darapladib have shown that darapladib produces substantial inhibition of Lp-PLA2 activity in the presence of intensive statin therapy and suggest that such intervention might result in additional systemic anti-inflammatory effects. Future studies are required to determine whether chronic Lp-PLA2 inhibition will stabilize high-risk lesions and potentially reduce CV events [26].

Combination therapy

Statins are the mainstay of lipid-lowering therapy in contemporary medicine because of their well-established efficacy for reducing cardiovascular disease morbidity and mortality in various at-risk populations. Patients who fail to achieve the LDL-C target with a regular dose of strong statins have the option of increasing the statin dose or combining the statins with other classes of lipid-lowering medications such as ezetimibe, bile acid sequestrants, fibrates, or ω 3-fatty acids [27,28].

However, residual risk of cardiovascular disease exists even in patients achieving LDL cholesterol goals [2]. Current therapeutic use of statins as monotherapy is still leaving many patients with atherogenic dyslipidemia at high risk for coronary events because even intensive statin therapy does not eliminate the residual cardiovascular risk associated with low HDL-C and/or high triglycerides. As compared with statin monotherapy (effective mainly on LDL-C levels and plaque stabilization), the association of a statin with a fibrate will also have a major impact on triglycerides, HDL and LDL particle size. Combined fibrate/statin therapy is more effective in achieving a comprehensive lipid control and may lead to additional cardiovascular risk reduction, as could be suggested for fenofibrate following ACCORD Lipid study subgroup analysis and for bezafibrate on the basis of one small randomized study and multiple observational data. Therefore, in appropriate patients with atherogenic dyslipidemia fibrates- either as monotherapy or combined with statins-are consistently associated with reduced risk of cardiovascular events [29,30].

The combination of fenofibrate with simvastatin, atorvastatin and rosuvastatin resulted in greater improvement of the overall lipid profile compared with the corresponding statin dose. The long-term efficacy of fenofibrate combined with low-or moderate-dose statin has been demonstrated in a wide range of patients, including patients with type 2 diabetes mellitus, metabolic syndrome, or elderly subjects. A recent trial randomized patients to receive fixed-dose combinations of fenofibrate 135 mg/day with rosuvastatin 5, 10 or 20 mg/day or to monotherapy with simvastatin 40 mg/day. The combinations resulted in significantly greater decreases in plasma levels of LDL-C, non-HDL-C, apoB, TG, hsCRP, VLDL-C, TC, and apoC-III, and a significantly greater increase in HDL-C concentration, compared with simvastatin 40 mg/day. For example the reductions in LDL-C levels with fenofibrate + rosuvastatin 5, 10 and 20 mg/day were 38.9%, 46.0% and 47.2% respectively compared with 32.8% for simvastatin 40 mg/day ($p < 0.01$) [31].

The principal differences between bezafibrate and other fibrates are related to its effects on glucose level and insulin resistance. A large number of studies showed beneficial effects of bezafibrate on glucose and insulin metabolism [32,33]. These effects could be primarily related to the direct influence of bezafibrate on insulin sensitivity via PPAR gamma. Triglyceride-lowering and HDL-C-raising effects of bezafibrate lead to decreased systemic availability of fatty acids, diminished fatty acid uptake by muscle with improvement of insulin sensitization, contributing also to a reduction of plasma glucose levels [34,35]. However the role of free fatty acids (FFAs) extends beyond their ability to induce or exacerbate insulin resistance and inflammation: they may contribute directly to the deterioration of beta cell function that accompanies the development of diabetes [36]. Lipotoxicity and glucotoxicity share many common features, and FFAs and glucose metabolism are intimately linked through their ability to act as competing oxidative substrates. Probably, reducing the chronic secretory demands for pancreatic beta-cell by improving insulin sensitivity and direct reducing of triglycerides and FFA accumulation in pancreatic islets can explain preservation of beta cell function in patients with T2DM treated with bezafibrate. Bezafibrate has a modest but significant beneficial effect on HbA1C.

This effect was observed irrespective of diabetes drug administration, but with a strong positive relationship between triglyceride and HbA1c reduction. In the BIP, bezafibrate reduces the incidence and delays the onset of T2DM vs. placebo among different high-risk populations: patients with impaired fasting glucose (30% reduction) and obese patients even with normal fasting glucose levels (42% reduction) [34,35]. In addition, bezafibrate significantly increased adiponectin levels both in humans and rodents. This effect was mediated mostly via PPAR alpha, but also partially via PPAR gamma [37]. Therefore, a pharmacological intervention that simultaneously influences lipids and glucose metabolism can be particularly effective to reduce the incidence and delay the onset of T2DM in appropriate high risk patients. These data support our suggestion that on the whole body level a balanced synergism of all PPARs could be justified. Among major fibrates, bezafibrate appears to have the strongest effect on HDL-C [34,35].

Multiple studies showed that most popular statins - simvastatin, atorvastatin, and rosuvastatin - have deleterious effects on glycemic control. For example, in the CORONA trial statin users were at a 1.13-fold (95% CI, 0.86-1.50) greater risk of developing new-onset diabetes than patients taking placebo. In the JUPITER trial, the relative risk was even higher (1.25 [95% CI, 1.05-1.49]) [38,39]. In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, new-onset T2DM developed in 166 of 1,905 patients randomized

to atorvastatin 80 mg/day and in 115 of 1,898 patients in the placebo group (8.71%vs.6.06%, adjusted HR:1.37, 95% CI:1.08 to 1.75, p=0.011). It should be pointed out that a newest statin-pitavastatin-seems to be better in this issue in the post-hoc LIVES study sub-analysis [40]. Still, the cardiovascular benefits of statin therapy clearly outweigh the risk of developing diabetes. However, the data suggest the need to make patients aware of this possible risk and to monitor patients for eventual development of diabetes, especially on intensive-dose therapy. In addition, concerns regarding new-onset diabetes should not be neglected due to the serious economic burden which this condition presents now. Moreover, based on the beneficial effects of pan-PPAR agonist bezafibrate on glucose metabolism and prevention of new-onset diabetes (about 30-40% risk reduction), one could expect neutralizing of the adverse pro-diabetic effect of statins (up to 25% increased risk). Therefore, a combined bezafibrate/statin therapy will be more effective in achieving a comprehensive lipid control, residual cardiovascular risk reduction and theoretically could prevent statin induced new-onset diabetes. The simvastatin and bezafibrate combination was found to be more efficacious than a single medication for treatment of diabetic dyslipidemia, as evidenced by improvement in the lipoprotein profile, reductions in Lp(a) and fibrinogen, and almost no clinically significant side-effects [38,41,42].

Recently, new data regarding statin/fibrate combination were published using the high quality comprehensive nationwide Acute Coronary Syndrome Israeli Surveys (ACSIS) registry. Development of 30-day major acute coronary event (MACE) - primary end-point - was recorded in 6.0% patients from the statin monotherapy group vs. 3.2% from the combination group, (p=0.01). The 30-day re-hospitalization rate was also significantly lower in the combination group. Multivariate analysis identified the fibrate/statin combination as an independent predictor of 46% reduced risk of MACE in overall population (p=0.03) [43].

Obviously, we must not forget the side effects whose risk at statin-fibrate combination therapy multiplies. Primarily this concerns possible increased incidence of muscle tissue damage and liver damage. Cerivastatin was voluntarily withdrawn from the market in August 2001 because of 31 deaths related to severe rhabdomyolysis [44]. Staffa reported fatal rhabdomyolysis to be 16–80 times more frequent with cerivastatin compared with other statins. Twelve of the original cases involved concomitant therapy with the fibrate gemfibrozil. Pharmacokinetic studies evaluating gemfibrozil administered with various statins revealed an increase in serum concentrations of all statins studied, (ie, cerivastatin, pravastatin, rosuvastatin, simvastatin) except fluvastatin. The publication utilizing reports from the Food and Drug Administration (FDA) showed that the combined use of gemfibrozil and a statin resulted in 590 cases of rhabdomyolysis compared with 16 with fenofibrate and statin therapy [45]. The majority of cases with both gemfibrozil and fenofibrate also involved cerivastatin. When considering the number of prescriptions dispensed during that timeframe, this indicates an approximate 20-fold increase with the gemfibrozil/statin regimen compared with the fenofibrate/statin combination. The findings nevertheless strongly suggest a greater rate of rhabdomyolysis with cerivastatin and also the combined use of statin therapy with gemfibrozil. The above information clearly points out the risks, particularly of myopathy, that can be associated with combination therapy. However, the risk of severe myopathy can be greatly reduced if appropriate measures are taken. The American College of Cardiology along with the American Heart Association and the National Heart, Lung and Blood Institute published a clinical advisory shortly after the

cerivastatin withdrawal, identifying concomitant medications that may predispose patients to statin-induced myopathy [46].

Conversely; on the basis of several studies, the fenofibrate has the smallest myopathic potential from fibrates and therefore, it can be used for treatment with a statin to achieve the target lipid levels. It should be mentioned that even with the triple combination of fenofibrate with atorvastatin/ezetimibe there was no significant difference in the rate of serious or treatment-related adverse events (AEs) and the overall incidence of such events was low. Furthermore, in elderly subjects the safety profile of fenofibrate+rosuvastatin administration was generally similar with the individual monotherapies [47]. To reduce the myositis risk with statin - fibrate combination therapy, it is recommended to use a lower statin dose (but in accordance with the guidelines), do not use the combination in the case of renal insufficiency and concurrent treatment with certain drugs. Combination therapy also requires the caution in patients at the age over 70, especially in women.

Mechanism of statin myopathy is not fully explained yet, but most likely involves the reduction of coenzyme Q10 (CoQ10). The objective of this study was to evaluate the possible benefits of coenzyme Q and selenium supplementation administered to patients with statin-associated myopathy (SAM). In conclusion, supplementation of statin-treated patients with CoQ10 resulted in a decrease in the symptoms of SAM, both in absolute numbers and intensity. Additional selenium supplementation was not associated with any statistically significant decrease of SAM. However, it is not possible to draw any definite conclusions, even though this study was carried out in double-blind fashion, because it involved a small number of patients [8].

Over the past several years, proprotein convertase subtilisin kexin type 9 (PCSK9) has gained significant attention as a key regulator of serum LDL-C levels. In humans, gain-of-function mutations result in significantly decreased LDL-C and cardiovascular risk. PCSK9 is a protease made and secreted by the liver into the plasma, which then binds to and causes the degradation of hepatic LDL receptors (LDL-R). This concept that PCSK9 acts as a secreted protein to bind the hepatic LDL-R and causes its degradation is supported by recent findings that disruption of this binding using anti-PCSK9 antibody results in preserved LDL-R and decreased LDL-C [48,49].

Conclusion

Currently, statins have dominant role in the treatment of dyslipidaemia. Statins significantly reduce LDL cholesterol, but when it comes to influencing the levels of triglycerides and HDL cholesterol, their effect is substantially smaller. This is a serious problem, especially in patients with atherogenic dyslipidaemia, characteristic in patients with metabolic syndrome.

On the other hand, among available pharmaceuticals, fibrates influence the above stated parameters the most, however, the influence on the level of LDL cholesterol is only minimally (depending on the initial level of triglycerides). The combination of statins and fibrates therefore represents an advantageous way of complementary influence on the lipid profile. In addition, it also brings significant pleiotropic effects (mainly influencing of endothelial dysfunction, anti-inflammatory and antithrombotic effect, by some there is also the possibility of potentiation of these effects), which are ultimately together with influencing of the lipid profile responsible for benefits documented in randomized controlled clinical studies.

Obviously, the patients with the combination therapy may

have increased risk of adverse reactions (especially myopathy and hepatotoxicity), therefore it require careful monitoring.

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