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SIGNIFICANT REDUCTION OF RESIDUAL CARDIOVASCULAR RISK WITH COMBINATION THERAPY WITH STATIN AND FIBRATE

ZNAČAJNA REDUKCIJA REZIDUALNOG KARDIOVASKULARNOG RIZIKA KOMBINOVANOM TERAPIJOM STATINOM I FIBRATOM

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Abstract

Despite achieving the desired LDL cholesterol values, patients remain at high residual risk of major macrovascular events. High TG and low HDL cholesterol are strong independent predictors of adverse cardiovascular events, regardless of LDL cholesterol levels, elevated TG and low HDL cholesterol. Patients with increased TG and decreased HDL-c benefit from a combination of statin and fibrate therapy. It is necessary to underline the fact that high doses of statins can further worsen, ie. reduce the HDL fraction (so-called „good cholesterol"), and that fenofibrates are the ones that can raise HDL concentrations. Also, fenofibrate is crucial for lowering triglyceride concentration, statins have very little effect in this regard. So, if the patient is indicated to introduce both drugs, our choice is always on a fixed combination because of all the advantages of taking one tablet. Therapy should be continuous, because we stabilize fatty plaques in the walls of blood vessels continuously, so that physiological concentrations of lipids in the circulation are not an indication for discontinuation of the drug, because there is a repeated disturbance of lipid status and a pronounced „rebound" phenomenon.

Key words

residual cardiovascular risk,
ombination with statins and fibrates

Ključne reči

rezidualni kardiocaskularni rizik,
kombinovana terapija
hiperlipoproteinemija

Residual cardiovascular risk reduction

In order to analysis the reduction of residual cardiovascular risk by hypolipidemics, it is important to point out two facts:

a) Changes in coronary blood vessels go through several stages:

Type 1-intima thickening

Type 2-fat stripes

Type 3 - transitional (intermediate) lesions

Type 4- advanced atheroma with a well-defined region of intima

Type 5 - fibroateroma (atheroma covered with a layer of connective tissue); angiographically registered as stenosis;

Type 6-complicated plaque with superficial defects and / or hematoma, and / or thrombosis; angiographically is registered as an occlusion [1-2].

High levels of TG increase the production of VLDL particles in the liver. Since VLDL is converted to LDL in the circulation, a high concentration of VLDL particles leads to a high concentration of LDL particles. These LDL particles with significant atherogenic potential are easily taken up by macrophages, which contributes to the formation of atherosclerotic plaque [1-2].

b) Arterial blood vessel remodeling and coronary stenosis are two temporally successive processes leading to the significant stenosis.

Pathohistological analyzes have shown that even in seemingly normal segments of coronary blood vessels, there may be atherosclerotic plaques. These plaques appear angiographically only when they obstruct 40% of the lumen of the artery. The effect of statins is not in the regression of these plaques, but in their stabilization (functional improvements due to the reduction of the number of macrophages and lipids) [1-2]. That is why it is important to aggressively treat dyslipidemias from the beginning, in order to intervene in the subclinical phase of the disease.

Treatment includes non-pharmacological and pharmacological measures. Non-pharmacological measures include hygienic-dietary regime, pharmacological drug therapy with statins, fibrates and their combination according to indications [1-3].

Why is it important to treat dyslipidemia?

From the point of view of cardiologists, it is important to emphasize that cardiovascular diseases are the leading cause of early mortality and disability in Europe, and the frequency is growing in developing countries as well. The main clinical entities are coronary heart disease (KB), ischemic stroke (MU), and peripheral arterial disease (PAB). The causes of these CVD are multifactorial. Some of these lifestyle factors (smoking, lack of physical activity, eating habits) can be modified. Other risk factors, such as high blood pressure, glycoregulation, and dyslipidemia, require intervention but can also be modified, while others (such as age and gender) are not modifiable [3-4].

Dyslipidemias, as a factor that can be modified, may have different significance in certain subgroups of patients. The group of atherogenic lipoproteins includes LDL cholesterol, IDL cholesterol and VLDL cholesterol. Antiatherogenic lipoproteins include non HDL-c as representing the difference between total cholesterol and HDL cholesterol. Non-HDL-c may be a better marker of CV risk compared to the LDL fraction in patients with high TG and diabetes, metabolic syndrome, or chronic renal failure (HBI) [1-7].

Elevated values of total cholesterol (UH) and low-density cholesterol (LDL-C) attract the most attention, so that the regulation of UH and LDL-C levels remains the main goal of dyslipidemia therapy [4-6]. Apo B is the main apolipoprotein that is part of atherogenic lipoproteins (VLDL, IDL, LDL), and the concentration of apo B is a good indicator of their presence in plasma. This is especially important in the case of high concentrations of small dense LDL particles. Several prospective studies have shown that apo B is equal to LDL-C in the prediction of cardiovascular risk. Apo B has not been investigated as a primary target in statin studies, but several post-hoc analyzes from statin studies suggest that apo B is not only a risk marker, but may be a better therapeutic target than LDL-C. The influence of triglycerides in the spectrum of risk factors for CVD is also significant. It is desirable to achieve TG values that are less than 1.7 mmol / l. There is still controversy as to whether the effect of TG values on the risk of CVD is due to the presence of residual particles - small dense LDL particles, or low HDL-C values. However, although the role of TG values as a risk factor for CVD remains completely unclear, TG values <1.7 mmol / l are considered desirable values; therapy is recommended at TG values> 2.3 mmol / l, with postprandial hypertriglyceridemia being a more precise predictor of the risk of developing cardiovascular disease compared to triglyceride concentration levels [3-11].

What are the target values of lipid status parameters?

Lipid status in adults was defined through desirable and risky values of lipid fractions (Table 1).

Table 1 *Recommended and risk values lipid parameters in adults (stricter criteria for people with cardiovascular disease, diabetes and metabolic syndrome)*

Lipid fractions	Recommended (mmol/l	High risk (mmol/l)	Very high risk (mmol/l)
Total Cholesterol	<5,2	5,2-6,19	≥6,2
Triglcerides	< 1,7	1,7-2,29	≥2, 3
HDL Cholesterol	≥1,6	1,0-1,6	≤ 1,0
LDL Cholesterol	<3,4	3,4 – 4,1	≥4,1
non HDL Cholesterol	<3,4	3,4 – 4,1	≥4,9

No target values have been established for HDL-C or triglycerides in clinical studies, although an increase in HDL-C predicts regression of atherosclerosis, and low HDL-C levels are associated with higher CV events and mortality in patients with coronary heart disease, even when LDL-C lower than 1.8 mmol / L. Recommended values for HDL: men> 1.0 mmol / l, women> 1.2 mmol / l. Recommended TG values: <1.7 mmol / l while therapy is recommended at TG values> 2.3 mmol / l. Given the lack of evidence from clinical studies on the efficacy of interventions for these lipid parameters to further reduce CV risk, they are considered secondary and optional goals of therapy [3-11].

Non-HDL-c is also recommended as a secondary target in the treatment of dyslipidemias. The target level of non-HDL is calculated by the formula: target value of LDL cholesterol + 0.8 mmol / L. Non-HDL-c should be used as a marker to treat residual CV risk in patients with atherogenic dyslipidemia, when LDL-C targets have been reached. The recommended non-HDL-C values are less than 2.6 mmol / L in patients at very high risk (in patients with T2DM and CV disease or chronic kidney disease and over 40 years without CV disease, or who have at least one CV risk factor of diseases or damage to target organs) or less than 3.0 mmol / L in high-risk patients (all patients with T2DM) [3-11].

The results of a recent meta-analysis involving 62,154 patients from 8 statin-treated studies indicate that patients who achieved LDL-C targets without reaching non-HDL target levels had a 32% higher risk of developing CVD compared with those who achieved target levels for both parameters (LDL-c and non-HDL-C) [11]. From all the above, there is a need to achieve both primary and secondary goals of treatment of dyslipidemia, because in this way the most optimal effect on the reduction of cardiovascular risk is achieved.

Atherogenic dyslipidemia: definition and significance

Atherogenic dyslipidemia is defined as a special lipid profile in patients with diabetes (elevated triglycerides, decreased HDL, elevated concentrations of small, dense LDL particles) and is an independent cardiovascular risk

factor, more potent than isolated high concentrations of triglycerides or low HDL cholesterol. It is important to emphasize that, due to the change in the protein component, the protective role of HDL cholesterol in these patients is lost. This lipid profile is typical for patients with type 2 diabetes, metabolic syndrome, and patients with pre-existing cardiovascular disease. Regulating LDL cholesterol levels does not reduce the residual vascular risk associated with low HDL cholesterol and elevated TG. Atherogenic dyslipidemia is a significant factor in the development of macro- and microvascular residual risk and is associated with the pathogenesis of microvascular complications in patients with type 2 diabetes, with a high prevalence even among statin-treated patients. Only 2.4% of statin-treated patients achieve target triglyceride and HDL cholesterol values [12-16].

Residual vascular risk (macro and microvascular)

Residual risk represents a significant risk of macrovascular events and microvascular complications that persists despite optimal correction of the cluster of cardiometabolic parameters. This optimization includes:

1. achieving the target values of LDL cholesterol (<2.5 mmol / l, or 1.8 mmol / L if there is cardiovascular disease);
2. intensive control of arterial blood pressure (systolic pressure less than 140 mmHg; diastolic pressure less than 90 mmHg);
3. intensive control of glycoregulation (3.5 - 5.6 mmol / l) [3,11].

Although LDL cholesterol targets were achieved with statin therapy (<1.8 mmol / L), patients with elevated triglycerides or low HDL cholesterol had a significantly higher risk of CV events than those with normal triglyceride and HDL values. Elevated triglycerides and low HDL contribute to the occurrence of residual cardiovascular risk in patients with dyslipidemia and / or type 2 diabetes, who remain exposed to a significant residual risk of:

1. macrovascular events (myocardial infarction, stroke);
2. microvascular complications (retinopathy, nephropathy, neuropathy).

Therefore, it has been suggested that non-HDL-c should be used as a correlate of residual CV risk in patients with atherogenic dyslipidemia, when LDL cholesterol targets have been reached [11-16].

Triglycerides and atherogenic potential

The prevalence of low HDL-c and high TG in patients with proven CVD has been evaluated in numerous studies and has shown the importance of atherogenic dyslipidemia as a potential risk factor [16-23].

Combinations of high levels of LDL cholesterol and high levels of triglycerides and low levels of HDL cholesterol and high levels of triglycerides are strong independent factors for the occurrence of major cardiovascular adverse events. Elevated triglycerides and low concentrations of HDL cholesterol have a negative synergistic effect on residual CV risk in patients with LDL cholesterol targets. High triglyceride concentrations are directly associated with higher mortality rates and high CV events which at the same time exacerbate low HDL cholesterol levels [16-25].

How to reduce the residual cardiovascular risk since increasing the statin dose is not effective?

Even intensive cholesterol lowering therapy with 80 mg atrovastatin reduces the absolute cardiovascular risk by only 2.2% compared to 10 mg atrovastatin [20]. Statins and fibrates have complementary effects on improving the lipid profile . When combined, they can help correct the concentrations of LDL cholesterol, triglycerides and HDL cholesterol, with the ultimate positive effect on lipid status [5-6, 11, 22-23].

Guidelines and recommendations for combination therapy

Patients with diabetes die from cardiovascular diseases two to four times more often than patients without diabetes with similar demographic characteristics. Despite achieving the target values of LDL cholesterol, patients with type 2 diabetes with elevated triglycerides and low HDL have a 70% higher risk of a large vascular event than those without lipid disorders, so more potent cardioprotection of these patients is necessary [23-24]. Several meta-analyzes have confirmed the clinical benefits of fibrates in major cardiovascular events, and this effect is most likely associated with an improvement in triglyceride levels [18-19, 23-24]. The addition of fenofibrate to a statin significantly improves the concentration of triglycerides and HDL cholesterol, with optimal control of LDL concentration. This combination has been shown to significantly reduce cardiovascular events (by 31% in patients with type 2 diabetes), with good long-term tolerability with a comparable safety profile compared to statin monotherapy [18-19, 23-24].

It is recommended that patients at very high risk (patients with T2DM and CV disease or chronic kidney disease and older than 40 years without CV disease, or who have at least one CV risk factor for disease or damage to target organs) in both primary and secondary prevention as targeted have an LDL-C concentration <1.4 mmol / L and at least a 50% reduced LDL concentration relative to baseline. In high-risk patients (all patients with T2DM), the target LDL-C value is <1.8 mmol / L with a reduction of at least 50% of the baseline registered concentration. The recommendations go further; if the patient recovers from a recurrent vascular event in the next 2 years (not necessarily of the same type as the primary event), at the maximum tolerable statin concentration, the target LDL-C <1.0 mmol / L may be considered. Recommended values for HDL are> 1.0 mmol / l for men and> 1.2 mmol / l for women. Preferred values are TG values <1.7 mmol / l; therapy is recommended at TG values> 2.3 mmol / l, with postprandial hypertriglyceridemia being a more precise predictor of the risk of developing cardiovascular disease compared to triglyceride concentration levels. Non-HDL-c should be used as a marker to treat residual CV risk in patients with atherogenic dyslipidemia. non-HDL-C <2.6 mmol / L is the recommended target value in very high-risk patients, and <3.0 mmol / L in high-risk patients [3-4] (Table 2).

Table 2 *Recommended values of lipid parameters in adults considering vascular risk*

Lipid fractions	High risk (mmol/l)	Very high risk (mmol/l)
Total Cholesterol	<1.8	<1.4 (<1.1)
Triglcerides	<1.7	
HDL Cholesterol	>1.0 for males, >1.2 for females	
LDL Cholesterol	<3.0	<2.6

Statin therapy should be initiated at lower doses if there is significant renal impairment and / or the potential to interact with other drugs, and then the dose should be titrated until the target LDL-C value for the given risk level is reached. Statin therapy alone is not sufficient to neutralize vascular risk attributed to elevated triglycerides and low HDL cholesterol. Patients with increased TG and decreased HDL-c benefit from a combination of statins and fibrates. It is necessary to emphasize the fact that high doses of statins can further worsen, ie. reduce the HDL fraction (so-called „good cholesterol"), and that fenofibrates are the ones that can increase the concentrations of HDL cholesterol. Also, fenofibrate is crucial for lowering triglyceride concentrations; statins have little effect in this regard. In high-risk patients with an achieved LDL-C target value and a TG concentration> 2.3 mmol / L, fenofibrate or bezafibrate may be considered in combination with statins. Fibrate, especially fenofibrate, due to its low potential for myopathies, may be prescribed concomitantly with statins in patients with atherogenic combined dyslipidemia, especially associated with diabetes and / or metabolic syndrome. in serum higher than 2.3 mmol / l, and when HDL cholesterol is low, especially when retinopathy is present. According to current recommendations, the combination of statins and fibrates results in a significantly greater decrease in the LDL fraction of cholesterol and an increase in the HDL fraction, compared to individual monotherapy [4-5, 25-26]. Fibrate, especially fenofibrate, due to its low potential for myopathies, may be prescribed concomitantly with statins to improve the achievement of lipid target values, in patients with atherogenic combined dyslipidemia, especially associated with diabetes and / or metabolic syndrome. Fenofibrate should be added to therapy in patients with diabetes when serum triglycerides are higher than 2.3 mmol / l, and when HDL cholesterol is low, especially when retinopathy is present [4-5, 6-7, 9-11]. In patients with diabetes, the target values of the individual lipid fractions are given in Table 3.

Table 3 *Recommended lipid fractions concentratations in patients with diabetes*

Lipid fractions	Recommended	Pay attention to
LDL cholesterol	<2 mmol/l	<1,8 mmol/l with cardiovascular comorbities
Triglycerides	<2,3 mmol/l	
HDL cholesterol	> 1 mmol/l	
non HDL cholesterol	<3,0 mmol/l	In high risk patients (all with type 2 diabetes); ≤ 2,5 mmol/l in *very high risk patients

* in patients with T2DM and cardiovascular diseases or chronic renal failure and older than 40 wih no CVD, or with at least one CV risk factor for disease or target organ damage

Safety of statin-fibrate combination

Good long-term tolerability of the statin-fibrate combination with a comparable safety profile compared to statin monotherapy has been demonstrated in myositis and rhabdomyolysis. In general, fibrates are safe and easy to use, with fenofibrate being used with a statin [4-5]. The intensity of statin therapy is defined based on the average expected reduction in LDL cholesterol by specific statin and dose (Table 4).

Table 4 *Intensity of statin therapy based on the average expected reduction of LDL cholesterol by specific statin and dose*

High statin doses	Optimal statin doses	Low statin doses
Daily dose averagely reduced LDL-C for ≥50%	Daily dose averagely reduced LDL-C for 30-50%	Daily dose averagely reduced LDL-C for ≤30%
Atorvastatin (40*)-80 mg Rosuvastatin 20 (40) mg	Atorvastatin 10 (20) mg Rosuvastatin 10 (5) mg Simvastatin 20-40 mg Pravastatin 40 (80) mg Lovastatin 40 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg

Adapted from ACC / AHA 20132 Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (statin names and doses tested in randomized clinical studies and meta-analyzes, which showed a reduction in major cardiovascular events are bolded).

The combination of simvastatin / fenofibrate is a response to the needs of modern treatment of cardiac patients and represents the first fixed combination of statins and fibrates. The advantages of the fixed combination of statins and fibrates are the following: simple dosing, one tablet, once a day, regardless of the meal, better compliance, better therapeutic effect, effect on all three lipid fractions [25].

Further strategy in lipid disorder treatment

PCSK9 inhibition with fully human monoclonal antibodies shows to be a very promising method to decrease LDL-C levels in various patient groups (with or without familiar hypercholesterolemias, with or without statin intolerance and at various levels of cardiovascular risk) (26). The safety profile of PCSK9 antibodies appears to be excellent, but the long-term data and cardiovascular endpoint trials are needed before the implementation in clinical practice.

CONCLUSION

Despite achieving the desired LDL cholesterol values, patients remain at high residual risk of major macrovascular events. High triglycerides and low HDL cholesterol are strong independent predictors of adverse cardiovascular events, independent of LDL cholesterol levels. Statin therapy alone is not sufficient to neutralize vascular risk attributed to elevated triglycerides and low HDL cholesterol. Patients with increased TG and decreased HDL-c benefit from a combination of statins and fibrates. It is necessary to emphasize the fact that high doses of statins can further worsen, ie. reduce the HDL fraction (so-called „good cholesterol"), and that fenofibrates are the ones that can increase the concentrations of HDL cholesterol. Also, fenofibrate is crucial for lowering triglyceride concentrations; statins have little effect on it. So, if the patient is indicated to introduce both drugs, our choice is always on a fixed combination because of all the advantages of taking one pill. Therapy should be continuous, because the stabilization of fatty plaques in the walls of blood vessels, as the most important effect of treatment with hypolipidemics, is a continuous process, so achieving target concentrations of lipid fractions in the circulation is not an indication for discontinuation of the drug , because of so- called „rebound" phenomenon considering of worsening of lipid status.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

Sažetak

Uprkos postizanju željenih vrednosti LDL holesterola, pacijenati ostaju izloženi visokom preostalom riziku od velikih makrovaskularnih događaja.Visoki TG i nizak nivo HDL holesterola su snažni neuzavisni prediktori neželjenih kardiovaskularnih događaja, nezavisno od nivoa LDL holesterola.Terapija samo statinima nije dovoljna da bi pokrila vaskularni rizik pripisan povišenim TG i niskom HDL holesterolu. Pacijenti sa povećanim TG i smanjenim HDL-c imaju korist od kombinovane terapije statinom i fibratom. Potrebno je podvući i činjenicu da visoke doze statina mogu dodatno da pogoršaju tj. smanje HDL frakciju (tzv. „dobri holesterol “), a da su fenofibrati ti koji mogu da podignu koncentracije HDL. Takođe, fenofibrat je ključan za snižavanje koncentracije triglicerida, statini imaju jako mali efekat u tom smislu. Dakle, ako je indikovan pacijentu uvesti oba leka, naš izbor je uvek na fiksnoj kombinaciji zbog svih prednosti uzmanja jedne tablete. Terapija treba da bude kontinuirana, jer stabilizujemo masne plakove u zidovima krvnih sudova kontinuirano, tado da fiziološke koncentracije lipida u cirkulaciji nisu indikacija za ukidanje leka, jer dolazi do ponovnog poremećaja lipidnog statusa i izraženog tzv „rebound” fenomena.

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