LOW HIGH-DENSITY LIPOPROTEIN CHOLESTEROL AS THE POSSIBLE RISK FACTOR FOR STROKE

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SUMMARY – Recent evidence suggests that lower HDL-cholesterol (HDL-C) may worsen the atherosclerotic process by promoting inflammation and progression from subclinical lesion to clinical event. Carotid intima-media thickness (CIMT) is recognized as a marker of early atherosclerosis and used to predict future vascular events. Among the common lipid parameters, LDL has strongest relation with carotid plaque. Cumulative effect of achieving optimal levels of LDL-C, HDL-C, triglycerides and blood pressure is a reduced risk of recurrent stroke and major cardiovascular events. The protective effect of higher HDL-C is maintained at low levels of LDL-C. Studies have demonstrated a trend toward a higher risk of stroke with lower HDL-C and support HDL-C as an important modifiable stroke risk factor. In patients with recent stroke or transient ischemic attack and no coronary heart disease, only lower baseline HDL-C predicted the risk of recurrent stroke. Substantial amount of residual cardiovascular risk remains in patients treated with statins due to elevated triglycerides and low HDL-C, even when LDL-C is well controlled. Niacin promotes significant increase in HDL-C and reduces cardiovascular risk. By combining niacin with the LDL-lowering therapy of statins, the progression of atherosclerosis is slowed down and residual cardiovascular and risk of stroke is reduced. Non-pharmacological control of serum lipids includes regular physical activity and modification in daily diet. In primary prevention, when HDL-C is below the average and other risk factors are present, a statin added to non-pharmacological therapy is appropriate choice. Fibrate therapy may be appropriate in men with manifest coronary disease with isolated low HDL-C. If HDL-C remains low, with or without high triglyceride levels, a fibrate or niacin may be added.

Key words: *Brain infarction – blood; Brain infarction – diagnosis; Brain infarction – risk factors; Cholesterol – blood; Cholesterol, HDL – metabolism; Atherosclerosis – diagnosis; Atherosclerosis – pathology; Atherosclerosis – therapy*

High-Density Lipoprotein Cholesterol and Risk of Ischemic Stroke and Cardiovascular Events

Low HDL-cholesterol (HDL-C) concentrations are associated with an increased cardiovascular risk and may aggravate the atherosclerotic process by promoting inflammation. Lower HDL-C levels may potentially accelerate the progression from subclinical lesions to cardiovascular clinical events. Carotid intima-media thickness (CIMT) is used as a marker of early atherosclerosis that significantly correlates with the presence of coronary artery disease and is able to predict future cardio- and cerebrovascular (CV) events in patients with subclinical carotid atherosclerosis. An updated view of the HDL-C has shown that the macrophage scavenger receptor BI (SR-BI) plays an integral role in the catabolism of HDL-C. Up-regulation of this receptor reduces plaque formation in an LDL-receptor-deficient mouse model of atherosclerosis.

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Phospholipid transfer protein has also become a target of increased analysis, as its role in the maturation of the HDL particle has become better understood. *In vitro* data from a transgenic mouse model over-expressing this protein demonstrate that plasma from these animals exhibits a potentially anti-atherogenic reduction in macrophage uptake of cholesterol. Over-expression of phospholipid transfer protein also yielded substantial reductions in HDL-C. These decreases combined with diminished atherogenicity imply more efficient reverse cholesterol transport, perhaps through the enhanced generation of pre-beta HDL[38-40].

Prediction of Cardio- and Cerebrovascular Events in Patients with Subclinical Carotid Atherosclerosis and Low HDL-cholesterol

Prediction of cardio- and cerebrovascular events was assessed in patients with subclinical carotid atherosclerosis and low HDL-cholesterol. Results showed that lower HDL-C concentrations were associated with ischemic stroke, peripheral arterial disease or with the presence of any clinical event. Independent variables associated with the events with predictive role were elevated fibrinogen concentrations, family history of coronary artery disease, and lower HDL-C levels. These results further suggest a synergistic role of low-HDL-C and inflammation in the atherosclerotic disease progression from subclinical lesions to clinical events[1]. A low level of HDL-C has been identified as a risk factor for stroke. Reduction in stroke with gemfibrozil therapy in men with coronary heart disease and low HDL-C has been observed in The Veterans Affairs HDL Intervention Trial (VA-HIT). The trial objective was to determine whether treatment aimed at raising HDL-C and lowering triglycerides reduces stroke in men with coronary heart disease and low levels of both HDL and LDL-C. A total of 2531 men with coronary heart disease, with mean HDL-C 31.5 mg/dL and mean LDL-C 111 mg/dL, were randomized to gemfibrozil 1200 mg/d or placebo and followed up for 5 years. In the placebo group, there were 76 strokes (9 fatal) and in the gemfibrozil group 58 strokes (3 fatal). Relative risk reduction by 31% was observed and evident after 6 to 12 months in the gemfibrozil group. Patients with baseline HDL-C below the median may have been more likely to benefit from gemfibrozil treatment than those with higher HDL-C[2]. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a proinflammatory enzyme that can predict major cardiovascular events, independent of both traditional risk factors and other markers of inflammation. In plasma, Lp-PLA2 is predominantly bound to LDL, and higher activity levels of this enzyme are especially associated with small-size LDL particles that are more atherogenic than larger LDL particles. Lp-PLA2 is also associated with HDL and may migrate between LDL and HDL particles in the circulation. In contrast to the positive association of Lp-PLA2 with LDL, this particular phospholipase has been found to be negatively correlated with plasma HDL-C concentrations, suggesting that higher levels of Lp-PLA2 might especially be associated with proatherogenic processes that are predominantly associated with lower levels of HDL-C. Lipoprotein-associated phospholipase A2 has been shown in general populations to predict cardiovascular events. Increased Lp-PLA2 could predict CV events in the absence of high LDL-C, in a population with low HDL-C. Plasma Lp-PLA2 activity was measured at baseline and after 6 months in a study group of 1451 men with low HDL-C (32 mg/dL) and low LDL-C (110 mg/dL), randomized to either placebo or gemfibrozil therapy. After adjustment for major CV risk factors, a 1-SD increase in Lp-PLA2 was associated with a significant increase in cardiovascular events (HR 1.17). Although gemfibrozil reduced Lp-PLA2 only modestly (6.6%), at higher levels of Lp-PLA2 gemfibrozil produced a significant reduction in CV events. In VA-HIT, a population with low HDL-C and LDL-C, high Lp-PLA2 independently predicted CV events that were reduced by gemfibrozil[3]. Reduced serum HDL-C is also an independent risk factor for ischemic stroke in elderly men. A significant temporal and quantitative relationship was observed between HDL-C levels and acute ischemic stroke presentation in the study that included 191 patients with first ever acute ischemic stroke. The average HDL-C at presentation was 44.4 mg/dL. Patients with a history of diabetes mellitus had lower HDL-C levels than non-diabetics at the time of stroke admission. Traditional stroke risk factors (dyslipidemia, diabetes mellitus, hypertension, tobacco use, coronary artery disease, and myocardial infarction) were inversely associated with HDL-C levels. HDL-C decreased from pre-stroke (55.0 mg/

dL) to immediate post-stroke levels (44.4 mg/dL) by 18.1%. HDL-C levels increased between immediate post-stroke levels and follow-up testing (51.6 mg/dL) after 2.6 months by an average of 29.6%. Prior history of myocardial infarction diminished HDL-C depression at the time of stroke. Findings indicated that HDL-C may be an acute phase reactant or nascent biomarker of acute stroke susceptibility[4].

Association of Lipid Profile with Ischemic Stroke

Association of lipid profile with ischemic stroke was evaluated in the observational case control study. The relation of ischemic stroke with different components of serum lipids showed that ischemic stroke was more common after age 50. Male suffered more than female from ischemic stroke (male to female ratio = 2.57:1). Hypertension and diabetes mellitus were found to be significant risk factors for ischemic stroke. High level of serum total cholesterol and LDL-C showed a significant risk in ischemic stroke. Low level of HDL-C appeared as a significant risk factor indicating beneficial effect of HDL-C on atherosclerotic process. Serum triglyceride level showed no significant effect on ischemic stroke[5]. The influence of total cholesterol, HDL-C and triglycerides on the risk of cerebrovascular disease was evaluated in the Copenhagen City Heart Study. Total cholesterol was positively associated with the risk of non-hemorrhagic events, but only for levels >8 mmol/L, while the relative risk remained nearly constant for lower plasma cholesterol values. Plasma triglyceride concentration was significantly positively associated with the risk of non-hemorrhagic events. There was a negative log linear association between HDL-C and risk of non-hemorrhagic events[6]. High-density lipoprotein cholesterol and the risk of ischemic stroke mortality was evaluated during 21-year follow-up of 8586 men from the Israeli Ischemic Heart Disease Study. During the follow-up, 295 men died from cerebrovascular events (241 due to ischemic stroke). Individuals with fatal ischemic stroke had a marginally lower age-adjusted mean HDL-C (1.05 mmol/L) and a significantly lower age-adjusted mean percentage of serum cholesterol contained in the HDL fraction (19.3%) than counterparts surviving the follow-up period (1.06 mmol/L and 20.6%, respectively). In multivariate analysis, a low concentration of HDL-C appeared to be significantly predictive of ischemic stroke mortality[7]. The Northern Manhattan Stroke Study analyzed HDL-C and ischemic stroke in the elderly. The protective effect of a higher HDL-C level was significant among participants aged 75 or older and more potent for the atherosclerotic stroke subtype and among different racial or ethnic groups. HDL-C is an important modifiable stroke risk factor[8]. Different risk factors for different stroke subtypes and association of cholesterol showed that serum total cholesterol was inversely associated with the risk of intracerebral hemorrhage, whereas the risk of cerebral infarction was raised at concentrations ≥7.0 mmol/L. The risks of subarachnoid hemorrhage and cerebral infarction were lowered with serum HDL-C levels ≥0.85 mmol/L[9]. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Higher total and lower HDL-C levels were associated with an increased risk of ischemic stroke, especially certain stroke subtypes. The lowest levels of total cholesterol were associated with an increased risk of all hemorrhagic strokes[10]. HDL-C, total cholesterol, and the risk of stroke were analyzed in middle-aged British men; higher levels of HDL-C were associated with a significant decrease in the risk of nonfatal stroke. In contrast, elevated total cholesterol showed a weak positive association with nonfatal strokes. The marked inverse association between HDL-C and stroke seen in hypertensives emphasizes the importance of these modifiable risk factors for stroke. The beneficial effects of elevated HDL-C on nonfatal stroke were seen in both smokers and nonsmokers and were more evident in men with hypertension than in normotensives[11]. Relative contributions of baseline systolic and diastolic blood pressure, low- and high-density lipoproteins and triglycerides to the risk of recurrent stroke or first major cardiovascular event (MCVE) and their potential impact on the benefit of statin treatment were evaluated in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. The SPARCL trial randomized 4731 patients with recent stroke or transient ischemic attack (TIA) and no known coronary heart disease and LDL-C between 100 and 190 mg/dL to either atorvastatin 80 mg/d or placebo. After 4.9 years of follow-up, there were 575 primary end points (fatal and nonfatal stroke), including 491 ischemic strokes, and 740

MCVEs (stroke plus myocardial infarction and vascular death). In patients with recent stroke or TIA and no coronary heart disease, only lower baseline HDL-C predicted the risk of recurrent stroke. Baseline HDL-C, triglycerides, and LDL/HDL ratio were associated with MCVE. Only baseline HDL-C and LDL/HDL ratio were associated with an outcome ischemic stroke. Each 13.7 mg/dL increment in HDL-C was associated with a 13% reduction in the risk of ischemic stroke and each doubling of LDL/HDL ratio was associated with a 31% increase in the risk of ischemic stroke. Atorvastatin treatment was similarly effective regardless of baseline lipoprotein levels[12]. Relative and cumulative effect of lipid and blood pressure (BP) control was further analyzed in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial (SPARCL). There were 4731 patients with recent stroke or transient ischemic attack and no known coronary heart disease randomized to atorvastatin 80 mg *per* day or placebo. At each level of LDL-C reduction, subjects with HDL-C value above the median or systolic BP below the median had greater reductions in stroke and major cardiovascular events, and those with a reduction in triglycerides above the median or diastolic BP below the median showed similar trends. Optimal control was defined as LDL-C 70 mg/dL, HDL-C 50 mg/dL, triglycerides 150 mg/dL, and SBP/DBP 120/80 mm Hg. The risk of stroke decreased as the level of control increased in those achieving optimal control of 1, 2, 3 or 4 factors as compared to none. Results were similar for major cardiovascular events. Cumulative effect of achieving optimal levels of LDL-C, HDL-C, triglycerides and BP on the risk of recurrent stroke and major cardiovascular events was observed. Optimal control of LDL-C (70 mg/dL), triglycerides (150 mg/dL), BP (120/80 mm Hg) and having an HDL-C value above 50 mg/dL had a cumulative effect on reducing stroke and major cardiovascular events, with hazard ratios decreasing as optimal levels of 1, 2, 3 or 4 of these factors were achieved (P=0.0012 for stroke and P=0.0001 for major cardiovascular events). The protective effect of having a higher HDL-C was maintained at low levels of LDL-C[13]. In the cross-sectional study of 324 apparently healthy Japanese men, high levels of serum cholesterol and the risk of stroke were analyzed. T1-weighted, T2-weighted and FLAIR MR images were used to detect and discriminate silent brain infarcts (SBI). Serum cholesterol was significantly associated with SBI: total cholesterol-odds ratio (OR) 3.75; LDL-C, OR 2.54, and non-HDL cholesterol, OR 2.54. There was a tendency for a positive association of HDL-C with SBI after adjustment for age, smoking status, serum triglycerides, maximal IMT, obesity, hypertension, diabetes mellitus, hyperuricemia, coronary heart disease and lipid-lowering agent use. Serum cholesterol levels are associated with SBI independently of the known confounders[14]. Vascular cognitive impairment is an important cause of cognitive decline in the elderly. Vascular dementia can be caused by small-vessel disease (S-VaD) or by large-artery atherosclerosis with multi-infarct vascular lesions in strategic areas of the brain (M-VaD). Vascular and biochemical risk factors of vascular dementia after lacunar strokes (S-VaD) and after multi-infarcts in strategic areas (M-VaD) were evaluated in patients with both types of dementia. In 60 patients with S-VaD and 34 patients with M-VaD, the presence of vascular and biochemical risk factors was evaluated and compared to age- and sex-matched 126 controls without dementia. Coronary artery disease, atrial fibrillation, hypertension and strokes were observed more frequently in both groups. Of biochemical risk factors, hyperhomocysteinemia (associated with low levels of folic acid and vitamin B12) and low HDL-C levels were found in both forms of VaD[15].

The Role of HDL Cholesterol in Metabolic Syndrome Predicting Cardiovascular Events

Evaluation of differences in the levels of serum atherosclerotic and fibrinolytic markers and the prevalence of metabolic syndrome was performed among patients with subtypes of cerebral infarctions. Blood samples from 171 cerebral infarction patients were collected to determine the levels of high-sensitivity C-reactive protein, serum total homocysteine, serum plasminogen activator inhibitor 1 and lipoprotein A. Subjects were also screened for metabolic syndrome. Atherothrombotic infarction was most prevalent, followed by lacunar and embolic infarction. There were no statistically significant differences in serum marker concentrations. The proportion of metabolic syndrome varied significantly among the subtypes and was highest among patients with embolic infarctions

with the lowest HDL-C levels[16]. HDL cholesterol in metabolic syndrome can predict cardiovascular events. Metabolic syndrome has recently been claimed to be an important new risk factor for the occurrence of coronary heart disease (CHD) and cardiovascular disease (CVD) events. Analysis of the predictive role of metabolic syndrome for CHD and CVD events was performed in a population study using the same factors in a continuous fashion, with special emphasis on HDL-C. There were 2650 cardiovascular disease-free men and women aged 35-74 years, examined and followed-up for 12 years. The classic risk factors (sex, age, systolic blood pressure, serum cholesterol and smoking habits) were studied as predictors of CHD and CVD events, alone and with the contribution of other factors (HDL-C, blood glucose, serum triglycerides and waist circumference) included in metabolic syndrome. Metabolic syndrome produced a predictive significant relative risk of 1.67 for CHD events and 1.82 for CVD events, but considering its single risk factors, the only ones contributing to the prediction were HDL-C and systolic blood pressure. Analyses showed that metabolic syndrome did not add anything to the power of prediction beyond the role of the single risk factors treated in a continuous fashion, while the best predictive power was obtained using classic risk factors (sex, age, smoking habits, total cholesterol and systolic blood pressure) with the addition of HDL-C. The correlation coefficient between total and HDL-C was modest and this justifies the contemporary presence in the models of these two variables and presentation of the relationship between HDL-C and CHD or CVD risk for different levels of total cholesterol. At each level of total cholesterol, increasing values of HDL-C correspond to a declining CHD and CVD risk. The predictive power of metabolic syndrome is bound only to the presence of HDL-C and blood pressure and does not add anything to using the same risk factor treated in a continuous fashion[17]. Lipids and carotid plaque were assessed in the Northern Manhattan Study. Cross-sectional analysis to investigate the relation between blood lipids and carotid plaque and to determine the incidence and risk factors of stroke was performed in a multiethnic population with lipid measurements and B-mode ultrasound of carotid arteries. Plaque was present in 61% of the participants and the mean total cholesterol was 202±41 mg/dL. Multiple logistic regression results showed that only LDL-C was associated with carotid plaque. Neither HDL-C nor triglycerides independently predicted carotid plaque. Apolipoprotein B (ApoB) was associated with the risk of plaque, while apolipoprotein A1 (apoA1) was associated with a decrease in multiple plaques. Lipoprotein-A was associated with an increased risk of multiple plaques. The apoB/apoA1 ratio had strongest relation with carotid plaque. Among the common lipid parameters, LDL-C has strongest relation with carotid plaque. ApoB and apoA1 may be stronger predictors of subclinical atherosclerosis and better targets for treatment to reduce plaque formation and risk of CVD[18].

Dyslipidemia among Diabetic Patients with Ischemic Stroke

Dyslipidemia is a potential independent risk factor for cerebrovascular disease in patients with diabetes. A total of 1046 patients with type 2 diabetes were assigned to diabetes with stroke and diabetes without stroke groups. Diabetic patients suffering stroke displayed poorly-controlled lipid and lipoprotein profiles, including a significantly lower proportion of patients achieving intensified LDL-C target of <2.07 mmol/L, but also less adherence to therapy prescribed for dyslipidemia, when compared with diabetic patients without stroke. Diabetic women with stroke had significantly lower serum level of HDL-C and apoA1, higher LDL-C level and higher apoB/apoA1 ratio when compared with diabetics without stroke. Diabetic patients with ischemic stroke remained uncontrolled for dyslipidemia. Intensified LDL-C and overall lipid lowering are potential precautions taken against ischemic stroke among diabetic patients. For LDL-C, no significant difference between diabetic patients with and without stroke (47.5% *vs.* 43.9%, P=0.236) was found in the proportion of subjects who were controlled for LDL-C <2.6 mmol/L. For HDL-C, a significantly smaller proportion of diabetic subjects with ischemic stroke had HDL-C levels >1.0 mmol/L for men and >1.3 mmol/L for women. Moreover, the likelihood of triglycerides being controlled to <1.7 mmol/L was not significant in those with ischemic stroke (74.4%) compared with those without ischemic stroke (72.4%)[19]. The efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in

14 randomized trials of statins was evaluated in the meta-analysis performed by the Cholesterol Treatment Trialists' Collaborators. Both types of diabetes are associated with dyslipidemia. In type 2 diabetes, triglyceride concentrations are high but HDL-C concentrations tend to be low, whereas in type 1 diabetes triglyceride concentrations are generally lower than those in type 2 diabetes, and HDL-C levels are average or even high. In both diseases, the concentration of LDL-C in the blood is generally similar to the population average, although this apparently benign pattern can mask an increase in atherogenic small dense LDL particles. Results of a collaborative meta-analysis of 14 randomized trials of statin therapy showed that lowering LDL cholesterol by 1 mmol/L reduces the risk of major vascular events (defined as the composite outcome of myocardial infarction or coronary death, stroke, or coronary revascularization) by about one-fifth in a wide range of high-risk participants, largely irrespective of baseline lipid profile or other presenting characteristics including diabetes[20]. Evaluation of the atherogenicity of lipids with normal fasting glucose (NFG), impaired fasting glucose (IFG), and type 2 diabetes was performed in coronary patients. Triglycerides significantly increased, while HDL-C and LDL particle diameter significantly decreased from subjects with NFG 5.6 mmol/L over patients with IFG 5.6 mmol/L to patients with type 2 diabetes. Factor analysis revealed several factors in the patient lipid profiles, i.e. triglycerides, HDL-C, apoA1, and LDL particle diameter loaded high on an HDL-related factor, and total cholesterol, LDL-C, and apoB loaded high on an LDL-related factor. In patients with type 2 diabetes, the HDL-related factor was associated with significant coronary stenoses of 50%. Consistently, in the prospective study, the HDL-related factor but not the LDL-related factor proved significantly predictive for vascular events in patients with type 2 diabetes. The low HDL-C/high triglyceride pattern is associated with the degree of hyperglycemia. In coronary patients with type 2 diabetes, this pattern correlates with the prevalence of CAD and significantly predicts the incidence of vascular events. For all 750 patients, triglycerides steadily increased, while HDL-C and LDL peak particle diameter steadily and significantly decreased from patients with NFG, over patients with IFG, to patients with type 2 diabetes. Specific treatment of diabetic dyslipidemia is most promising to reduce cardiovascular events among patients with diabetes. With well tolerated extended-release formulations of niacin, it is now possible to improve the pattern of lipid abnormalities observed in patients with type 2 diabetes. Inhibition of cholesterol ester transfer protein activity with torcetrapib has recently been shown to increase HDL-C by as much as 106%[21]. Glycemic index is a determinant of serum HDL-C concentration. Diet influences the prevalence of coronary heart disease and insulin sensitivity and concentrations of HDL-C. Dietary carbohydrates with a high glycemic index cause a high postprandial glucose and insulin response, and are associated with decreased insulin sensitivity and an increased risk of CHD. Is the glycemic index of dietary carbohydrates a determinant of serum HDL-C concentrations? Dietary, anthropometric and biochemical data from the Survey of British Adults were reanalyzed by a multiple regression model and examined the relation between serum total cholesterol, HDL-C and calculated LDL-C concentrations and various dietary characteristics including the type of carbohydrate, the glycemic index, and fat intake. Among 1420 participants with complete data, there was a significant negative relation between serum HDL-C concentration and the glycemic index of the diet for both men and women. No other significant relation was found with total cholesterol or LDL-C concentration or with any other dietary carbohydrate or fat constituent. In a cross-sectional study of middle-aged adults, the glycemic index of the diet was the only dietary variable significantly related to serum HDL-C concentration. Thus, the glycemic index of the diet is a stronger predictor than dietary fat intake of serum HDL-C concentration[22].

Targeting Low HDL-Cholesterol to Decrease Residual Cardiovascular Risk

Several large trials and meta-analyses have consistently demonstrated that statin therapy significantly reduces LDL-C levels and incidence of cardiovascular events. In spite of the efficacy of statin therapy, statins do not eliminate cardiovascular risk completely. Significant residual cardiovascular risk remains after treatment with statins, especially in high-risk patients such as those with diabetes. Residual cardiovascular

risk stems partially from low HDL-C and elevated triglycerides. Low HDL-C levels have been identified as a significant, independent predictor of cardiovascular risk, and increases in HDL-C are associated with reductions in cardiovascular events. Low HDL-C is associated with high cardiovascular risk. The TNT trial investigated the efficacy of high-dose statin therapy compared with low-dose statin therapy in patients with stable CHD. Patients were randomized to receive either atorvastatin (80 mg) with a target LDL-C of 70 mg/dL, or atorvastatin (10 mg) with a target LDL-C of 100 mg/dL. Patients with lower LDL-C levels had an approximate 25% risk reduction of having a CHD event. If subjects had low LDL-C levels, they still had a very high rate of CHD events if they also had low HDL-C levels. With higher HDL-C levels, the CHD rate decreased significantly. Even for patients in the lowest stratum of LDL-C (≤70 mg/dL) after 3 months of statin treatment, there was an increased 5-year risk of major cardiovascular events if HDL-C levels were also low. The risk of a major cardiovascular event differed significantly among quintiles of HDL-C levels in which those patients in the highest HDL-C quintile (Q5 ≥55 mg/dL) had a lower risk of major cardiovascular events than patients in the lowest HDL-C quintile (Q1 <37 mg/dL). Combination therapy may be necessary to address multiple lipid targets (LDL-C, non-HDL-C, HDL-C, and triglycerides). Among 57 patients treated with extended release (ER) niacin/statin for 24 months, there was a significant regression in carotid IMT (-0.041 mm; $P<0.001$ *vs.* placebo/statin). ARBITER trial provided additional evidence to support the promise of long-term combination therapy in reducing cardiovascular risk. When ER niacin was added to statin therapy, there was a significant regression in atherosclerosis as measured by carotid IMT after both 12 and 24 months of treatment. In patients with diabetes or the metabolic syndrome, there was also a significant regression in carotid IMT (-0.046 mm; $P<0.001$ *vs.* placebo/statin) with ER niacin/statin after 12-24 months of treatment *versus* statin monotherapy. Adding niacin or a fibrate to a statin is a therapeutic option that should be considered. As monotherapy agents, fibrates and niacin have been demonstrated to alter several lipid parameters and reduce cardiovascular events. Niacin appears to exert the greatest beneficial effects on the widest range of lipoprotein abnormalities. Niacin/statin combination therapy may slow down atherosclerosis progression in CHD patients and reduce residual cardiovascular risk. Niacin is the most effective agent for raising HDL-C levels, and ER niacin/statin combination therapy may promote the cost-effective achievement of optimal lipid values[23]. Patients with CHD receiving long-term statin therapy and with LDL-C level under 100 mg/dL and HDL-C level under 50 mg/dL for men or 55 mg/dL for women, were randomly assigned to receive ER niacin (2000 mg/d) or ezetimibe (10 mg/d). The primary end point was between-group difference in the change from baseline in the mean common carotid IMT after 14 months. The mean HDL-C level in the niacin group increased by 18.4% over 14-months, to 50 mg/dL, and the mean LDL-C level in the ezetimibe group decreased by 19.2%, to 66 mg/dL. Niacin therapy significantly reduced LDL-C and triglyceride levels; ezetimibe reduced the HDL cholesterol and triglyceride levels. As compared with ezetimibe, niacin had greater efficacy regarding the change in the mean carotid IMT over 14 months, leading to significant reduction of both mean and maximal carotid IMT. Paradoxically, greater reductions in the LDL-C level in association with ezetimibe were significantly associated with an increase in carotid IMT. The incidence of major cardiovascular events was lower in the niacin group than in the ezetimibe group (1% *vs.* 5%; $P=0.04$ by χ^2-test)[24].

Non-pharmacological Control of Plasma Cholesterol Levels

Reviewing studies on chocolate and stroke involving 44,489 subjects taking one serving of chocolate *per* week showed the subjects that consumed chocolate to be less likely to have a stroke than those that ate no chocolate; the observed stroke risk reduction was 22%. People who consumed 50 g of chocolate once a week were by 46% less likely to die from stroke than people who did not eat chocolate[25]. Consumption of chocolate has been often hypothesized to reduce the risk of cardiovascular disease (CVD) due to chocolate's high levels of stearic acid and antioxidant flavonoids. Debate still lingers regarding the true overall long term beneficial cardiovascular effects of chocolate. Review of the English-language MEDLINE publications for experimental, observational, and clinical studies

of relations between cocoa, cacao, chocolate, stearic acid, flavonoids (including flavonols, flavanols, catechins, epicatechins, and procynadins) and the risk of CVD (coronary heart disease, stroke) has shown that cocoa and chocolate may exert beneficial effects on cardiovascular risk *via* effects on lowering blood pressure, anti-inflammation, anti-platelet function, higher HDL, and decreased LDL oxidation. Flavonoid content of chocolate may reduce the risk of cardiovascular mortality. Updated meta-analysis indicates that the intake of flavonoids may lower the risk of CHD mortality, RR=0.81 (95% CI: 0.71-0.92). Multiple lines of evidence from laboratory experiments and randomized trials suggest that stearic acid may be neutral, while flavonoids are likely to be protective against CHD mortality[26]. Regular aerobic physical activity generally induces an increase in plasma HDL-C and a decrease in plasma triglyceride levels. The effect on total and LDL-C is inconsistent and generally modest. This effect is dose-dependent and the efficacy threshold is set at 1500 kcal/week (equivalent to about 24 km of brisk walking or jogging *per* week). Aerobic physical activity such as walking, jogging, cycling or swimming, with total energy expenditure of 1500-2200 kcal/week (which corresponds to about 24-32 km of brisk walking or jogging *per* week) may increase plasma HDL-C levels by 3.5-6 mg/dL and lower plasma triglyceride levels by 7-20 mg/dL. Another 16 km/week would trigger an additional 3 mg/dL increase in plasma HDL-C levels and an additional 3-8 mg/dL drop in plasma triglyceride concentrations[27]. Interventions on other macro- and micronutrients have shown that ethanol consumption at doses that may be regarded as 'moderate' (30-40 g/day in men and 15-25 g/day in women) is associated with significantly higher HDL cholesterol levels than those found in non-drinkers. This effect is seen on both main HDL subfractions (HDL2 and HDL3) and may be directly elicited by ethanol through increased synthesis of apoA1, the major apolipoprotein present in HDL. High ethanol intake may sometimes increase plasma triglyceride levels, in particular in subjects already hypertriglyceridemic at baseline, but on an average the effect of moderate ethanol doses on plasma triglyceride levels is not significant. The action of ethanol on HDL lipoproteins may account for about half of the reduction in coronary and cardiovascular risk associated with moderate ethanol consumption in observational studies[27-30]. Improvements in HDL-C and plasma triglyceride levels tend to be greater in overweight or obese subjects on low carbohydrate diet, whereas changes in LDL-C levels were more favorable in subjects on low-fat diets. In most available studies, body weight control can reduce significantly, albeit not dramatically, plasma total and LDL-C levels, especially in obese subjects. A decline in triglycerides is usually observed; HDL-C levels tend to rise on sustained weight loss[27,31]. Incorporation of food products that contain 2 g of phytosterols into the diet reduces plasma total and LDL-C levels by about 10% without significant effects on plasma HDL-C and triglycerides. Their consumption should be linked to the principal meal and be continued for a long time[27]. Including 25 g of soy protein in the diet as partial replacement for animal protein reduces plasma total and LDL-C concentrations. The beneficial effects are proportionally greater in subjects with hypercholesterolemia; no significant effects are observed on HDL-C and plasma triglyceride levels. The most effective cholesterol-lowering soy component is almost certainly protein, whereas isoflavones do not appear to contribute significantly to the effects on lipid metabolism. The cholesterol-lowering effect may be attributable to the ability of soy protein to up-regulate the expression of apo-B receptors[27,32,33]. Absorbable dietary carbohydrates do not play a major role in the control of total and plasma LDL cholesterol levels, even though they can reduce the levels of these when they replace hypercholesterolemic fat, i.e. saturated and trans-fatty acids. On the other hand, low-GI foods may help ameliorate, although to a limited extent, plasma HDL cholesterol levels and reduce plasma triglyceride levels. A daily fiber intake of 25-30 g may play a significant hypocholesterolemic role; soluble and gel-forming fiber is more effective than non-soluble fiber, and increasing its intake by 5 g/day can reduce total and plasma LDL cholesterol levels[27].

Dietary Fatty Acids and Cholesterolemia

When isocalorically substituted for nutrients with neutral effects on cholesterolemia (such as carbohydrates), saturated and trans-fatty acids tend to increase total and plasma LDL cholesterol levels. Polyunsaturated, cis-fatty acids (those of the n-6 series such as linoleic acid) induce opposite effects. Monounsatu-

rates, such as oleic acid, also reduce total and plasma LDL cholesterol levels, although to a lesser extent than n-6 polyunsaturates. The effects of fatty acids on plasma HDL cholesterol levels include an increase after saturate intake; an increase (to a lesser degree) after monounsaturate consumption; no change after polyunsaturates; and a decrease after *trans* ingestion. A lipid intake of 30%-35% of total calories is probably adequate to control total and plasma LDL cholesterol; it is advisable to use mainly extra virgin olive oil as dietary fat of choice, even though its effects on total and plasma LDL cholesterol levels are modest. Saturate intake should be limited to 7%-10%, while *trans* intake should be limited to those from dairy products only. The use of seed oils rich in n-6 polyunsaturates improves total and plasma LDL cholesterol levels; polyunsaturates can contribute to up to 7%-10% of total calories, including 1% of n-3 polyunsaturates (which do not modify total and plasma LDL cholesterol levels)[27,34]. The most recent evidence puts a new perspective on the role of dietary cholesterol in cholesterolemia management. Even if it may seem advisable not to exceed daily cholesterol intake of 300 mg, it is unwise to reduce dramatically or eliminate cholesterol-rich foods such as eggs[27].

Treatment of Lipid Abnormalities

The treatment of lipid abnormalities for primary prevention of CHD should be undertaken after global risk assessment in the individual patient. Family history, age, sex, blood pressure and presence of diabetes, as well as specific lipid abnormalities such as elevated LDL-C or low HDL-C should all be considered. Drug therapy should be considered in patients with elevated LDL-C and at least two additional risk factors. In primary prevention, when HDL-C is below average and other risk factors are present, a statin added to non-pharmacological therapy appears to be an appropriate choice, with a goal of 130 mg/dL (3.36 mmol/L) or lower. Based on the Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial, fibrate therapy may be appropriate in men with manifest coronary disease with isolated low HDL-C. The target for LDL-C lowering should be a level below 100 mg/dL (<2.59 mmol/L). If HDL-C remains low, with or without high triglyceride levels, a fibrate or niacin may be added; however, the risks of such combinations, especially myopathy, should be considered[35-37].

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Sažetak

NIZAK HDL KOLESTEROL KAO MOGUĆI ČIMBENIK RIZIKA ZA MOŽDANI UDAR

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Novija istraživanja ukazuju da nizak HDL kolesterol može pogoršati aterosklerotski proces, pospješiti upalu i progresiju bolesti od subkliničke lezije do kliničkog događaja. Debljina stijenke karotidne arterije (engl. *intima-media thickness*, IMT) je prepoznata kao pokazatelj rane ateroskleroze i predskazatelj budućih vaskularnih događaja. Između lipidnih frakcija LDL ima najveću povezanost s karotidnim plakom. Kumulativni učinak postizanja optimalnih vrijednosti LDL i HDL kolesterola, triglicerida i krvnog tlaka rezultira smanjenjem rizika od ponovljenog moždanog udara i kardiovaskularnih događaja. Zaštitni učinak povišenog HDL se održava pri niskim vrijednostima LDL. Studije su pokazale trend prema povećanom riziku od moždanog udara pri niskim vrijednostima HDL te da je HDL važan modificirajući rizični čimbenik za moždani udar. U bolesnika s novijim moždanim udarom ili prolaznim ishemijskim napadajem (engl. *transient ischemic attack*, TIA) bez koronarne bolesti srca samo su niske bazične vrijednosti HDL su predskazatelj rizika za ponovljeni moždani udar. Značajan ostatni kardiovaskularni rizik zaostaje u bolesnika koji su se liječili statinima, i to zbog povišenih triglicerida i niskog HDL, iako su vrijednosti LDL dobro kontrolirane. Niacin značajno povećava HDL i smanjuje kardiovaskularni rizik. Kombinacija niacina i statina usporava napredovanje ateroskleroze, smanjuje ostatni kardiovaskularni rizik i rizik od moždanog udara. Nefarmakološka kontrola serumskih lipida uključuje redovitu tjelesnu aktivnost i promjenu prehrambenih navika. U primarnoj prevenciji kada je HDL ispod prosječnih vrijednosti i uz prisutnost ostalih čimbenika rizika statini se mogu dodati nefarmakološkoj terapiji. Terapija fibratima može biti prikladna u muškaraca s manifestnom koronarnom bolešću srca i izoliranim niskim vrijednostima HDL. Ako zaostanu niske vrijednosti HDL s povišenim trigliceridima ili bez njih, tada se u terapiju može dodati fibrati ili niacin.

Ključne riječi: *Moždani infarkt – krv; Moždani infarkt – dijagnostika; Moždani infarkt – čimbenici rizika; Kolesterol – krv; Kolesterol, HDL – metabolizam; Ateroskleroza – dijagnostika; Ateroskleroza – patologija; Ateroskleroza - terapija*