

# Lipoprotein profile in patients who survive a stroke

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## Abstract

**OBJECTIVE:** In the subjects, who survived a stroke, an atherogenic lipoprotein profile phenotype B, was identified and a predominance of atherogenic lipoproteins of the lipoprotein families, VLDL and LDL, in the lipoprotein spectrum, was confirmed. The higher total cholesterol, triglycerides, and low HDL concentrations were accompanied by high serum levels of small dense LDL – strong atherogenic subfractions of the LDL family. High LDL2 also contributes to the creation of the atherogenic lipoprotein profile. Conversely, decreased serum concentration of LDL1 suggests, that the LDL1 subfraction does not contribute to the creation of an atherogenic lipoprotein profile of specific individuals, i.e., those who survived a stroke.

**MATERIALS AND METHODS:** A quantitative analysis of serum lipoproteins in a group of stroke patients, and in a group of healthy normolipidemic volunteers, without signs of clinically manifested impairment of the cardiovascular system, was performed. For the analysis of plasma lipoproteins, an innovative electrophoresis method was used, on polyacrylamide gel (PAG) – the Lipoprint LDL system, (Quantimetrix corp., CA, USA). With regard to lipids, total cholesterol and triglycerides in serum were analyzed with an enzymatic CHOD PAP method (Roche Diagnostics, FRG). A new parameter, the score for anti-atherogenic risk (SAAR), was calculated as the ratio between non-atherogenic to atherogenic serum lipoproteins in examined subjects.

**RESULTS:** An atherogenic lipoprotein profile phenotyp B was identified in the individuals who survived a stroke. There were increased concentrations of total cholesterol, triglycerides ( $p < 0.001$ ), and atherogenic lipoproteins: VLDL ( $p < 0.001$ ), total LDL, LDL2 ( $p < 0.0001$ ) and LDL3–7 ( $p < 0.01$ ), in the group of stroke patients, compared to the control group. The LDL1 subfraction, like HDL, was decreased and did not contribute to the formation of the atherogenic lipoprotein spectrum in stroke-surviving individuals. Therefore, it can be assumed that the LDL1 subfraction is not an atherogenic part of the LDL family, which was usually considered to be an atherogenic lipoprotein part of the lipoprotein spectrum. Decreased SAAR values – score of anti-atherogenic risk, was confirmed in the stroke surviving individuals, compared to the controls, with high statistical significance ( $p < 0.0001$ ).

**CONCLUSIONS:** The advantages of this new method include:

- Identification of an atherogenic and a non-atherogenic lipoprotein profile, in the serum of examined individuals.
- Identification of an atherogenic normolipidemic lipoprotein profile; phenotype B in subjects who survived a stroke.
- Introduction of new risk measure, the score for anti-atherogenic risk (SAAR), to estimate the atherogenic risk of examined individuals.
- Declaration of an atherogenic lipoprotein profile is definitive when small dense LDL are present in serum. It is valid for hyperlipidemia and for normolipidemia as well.
- Selection of optimal therapeutic measures, including removal of atherogenic lipoproteins, as a part of a complex therapeutic approach, and the secondary prevention of a relapsing ischemic cerebral-vascular event.

#### Abbreviations:

APTT	- activated partial thromboplastin time
CE	- cardioembolism
CT	- computed tomography
ECG	- electrocardiography
HDL	- high density lipoproteins
INR	- international normalized ratio
LAA	- large-artery atherosclerosis
LDL	- low density lipoproteins
MRI	- magnetic resonance imaging
oxid-LDL	- oxidized LDL
PAG	- polyacrylamide gel
SAAR	- score for anti-atherogenic risk
SAO	- small artery occlusion
sdLDL	- small dense low density lipoproteins
OC	- stroke of other determined cause
UND	- stroke of undetermined cause
TOAST	- Trial of Org 10172 in Acute Stroke Treatment
TG	- triglycerides
VLDL	- very low density lipoproteins

## INTRODUCTION

The atherogenic serum lipoproteins in higher concentrations, VLDL and LDL, create an atherogenic lipoprotein constellation, which plays a key role in the acute onset of a cardiovascular and also of a cerebral-vascular event, i.e. stroke (Sarkar & Rautaray 2008; Shoji *et al.* 2009). Stroke is the leading cause of mortality and of long-term morbidity in populations of developed industrialized countries in the world. Stroke represents a heterogeneous group of diseases with more than 150 known causes. To date, in 25–39% of strokes, the cause, leading to the acute cerebral-vascular event, usually cannot be definitively explained (Amarenco *et al.* 2009). The reason for this is not merely a less than adequate examination choice or the use of analytical methods with low predictive prognostic values for stroke. It could also be attributable to our insufficient knowledge about

other co-morbidities in individuals who are susceptible to stroke and the incompletely explained pathophysiological inter-relations among these co-morbidities, as yet. There are several studies that provided evidence for the relation between a carotid stenosis and an ischemic cerebral event (Shoji *et al.* 2009); however, the causal inter-relation between dyslipidemia and stroke was not explained sufficiently, despite the fact that some studies recently reported evidence for the inter-relation between hypercholesterolemia and the development of a carotid stenosis (Amarenco *et al.* 2008; 2009; Vrablik 2009). The same can be said about essential hypertension, which is generally accepted as a risk factor for hemorrhagic and also ischemic cerebral-vascular events (Amarenco *et al.* 2008; 2009). There are some studies that confirm the relation between dyslipidemia and arterial hypertension, where the pathophysiological relation is explained much more particularly (Kalita 2006).

The cerebral stroke attack remains a frequent medical problem, and is the third most frequent cause of mortality all over the world. Stroke is also the most frequent cause of epilepsy onset in the older population and the most frequent secondary cause of the development of senile dementia. A frequent consequence of a stroke is depression. From an economics point of view, stroke is the fourth-frequent cause of a physical as well as mental disability and of the loss of self-sufficiency. Thus stroke is considered the second most expensive illness, from the point of view of the expenditure necessary for its treatment, as well as for the treatment of the possible severe health consequences after a stroke.

Relapsing ischemic strokes account for one-fourth of all strokes in a year, as a consequence of a failure in secondary prevention (Bejot *et al.* 2007). This hard reality leads rightly to the idea of optimal stroke prevention, i.e. to the selection of individuals, who are at risk of stroke. The identification of these at-risk individuals, follow-up with optimal prevention measures, including extensive education of the individuals at risk, could help to avoid the risk of death for these subjects, and increase the quality of life of those who survive stroke.

A new diagnostic electrophoretic method for lipoprotein analysis on polyacrylamide gel (PAG) – the Lipoprint LDL system, can quantify atherogenic and non-atherogenic lipoprotein populations and identify an atherogenic, or a non-atherogenic lipoprotein profile in examined subjects (Hoefner *et al.* 2001).

The aim of this pilot study was to identify and quantitatively evaluate atherogenic lipoproteins and to determine the lipoprotein profile phenotype in subjects who had suffered an ischemic cerebral-vascular event (stroke).

## PATIENTS AND METHODS

The pilot study included 56 patients (24 men; in average age, 64 years  $\pm$ 13 years and 32 women; average age, 74 years  $\pm$ 13 years), who survived an ischemic

cerebral-vascular event, i.e., a large-artery atherosclerosis subtype of stroke. To determine the subtype of ischemic stroke, the original TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria were used. The TOAST criteria classify patients with ischemic stroke into five core etiologic groupings: large-artery atherosclerosis (LAA); cardioembolism (CE); small artery occlusion (SAO); stroke of other determined cause (OC); and stroke of undetermined cause (UND). The diagnosis of subtype was based on the risk factor profiles, clinical features, and results of diagnostic tests, including CT scan/MRI, vascular imaging (carotid duplex, transcranial Doppler), ECG, echocardiography (transesophageal or transthoracic), and assessment of prothrombotic syndromes (Adams *et al.* 1993), (activated partial thromboplastin time (aPTT), and international normalized ratio (INR).

A group of subjects with newly diagnosed arterial hypertension was created from 45 individuals. Twenty-five males and 20 females with an average age of 36 years ± 6 years, were examined before any medication had been initiated.

A blood sample from an antecubital vein was obtained throughout the 24 hours after the onset of cerebral-vascular event.

The blood serum was obtained and a concentration of total cholesterol and triglycerides using the enzymatic CHOD PAP method (Roche Diagnostics, Germany) was analyzed. The quantitative analysis of

lipoprotein families and the lipoprotein subfractions, VLDL, IDL1–3, LDL1, LDL2, LDL3–7, HDL and the determination of a non-atherogenic lipoprotein profile, phenotype A, versus an atherogenic lipoprotein profile, phenotype B (Van *et al.* 2007), was performed by the Lipoprint LDL system (Quantimetrix Corp. CA, USA) (Hoefner *et al.* 2001).

The score for anti-atherogenic risk (SAAR) was calculated as a ration between non-atherogenic and atherogenic lipoproteins in plasma (Oravec 2007a). SAAR values over 10.8 represented a non-atherogenic lipoprotein profile, values under 9.8 represented an atherogenic lipoprotein profile.

A control group was created from 153 healthy normolipidemic volunteers, with no smokers, and without clinically manifested or chemically identified signs of cardiovascular, or cerebral-vascular diseases. The average age of examined subjects was 21.5 ± 2.5 years and the group involved 59 males and 94 females. Volunteers were recruited from students of medicine at the Medical school; they signed a study-information agreement,

**Tab. 1.** Total number of individuals who survived stroke, n=56

Atherogenic lipoprotein profile, phenotype B:	50 patients	89.3%
Non-atherogenic lipoprotein profile, phenotype A:	6 patients	10.7%

**Tab. 2.** Plasma concentration of lipids, lipoproteins, and score for anti-atherogenic risk (SAAR) in the group of stroke patients vs. the control group.

Stroke patients (n = 56)											
Chol	TG	VLDL	IDL1	IDL2	IDL3	LDL1	LDL2	LDL3-7	LDL	HDL	SAAR
<i>(mmol/l ± SD)</i>											
5.19	2.21	1.08	0.48	0.29	0.28	0.78	0.78	0.30	2.92	1.09	6.4
±1.10	±0.90	±0.35	±0.18	±0.13	±0.15	±0.36	±0.26	±0.24	±0.82	±0.32	±4.5
Control group (n = 153)											
Chol	TG	VLDL	IDL1	IDL2	IDL3	LDL1	LDL2	LDL3-7	LDL	HDL	SAAR
<i>(mmol/l ± SD)</i>											
4.34	1.15	0.62	0.39	0.27	0.33	0.93	0.40	0.03	2.34	1.34	38.9
±0.61	±0.53	±0.21	±0.12	±0.11	±0.12	±0.30	±0.20	±0.02	±0.41	±0.31	±20.0
Control. vs. Stroke											
..... p<0.0001 .....		p<0.003		n.s.	p<0.01	p<0.002	..... p<0.0001 .....				
Patients with newly identified arterial hypertension (n=45)											
Chol	TG	VLDL	IDL1	IDL2	IDL3	LDL1	LDL2	LDL3-7	LDL	HDL	SAAR
<i>(mmol/l ± SD)</i>											
5.06	2.28	0.91	0.45	0.39	0.31	0.77	0.69	0.38	2.99	1.26	9.1
±0.96	±0.89	±0.30	±0.18	±0.11	±0.12	±0.33	±0.28	±0.10	±0.77	±0.96	±4.8

and the study was approved by the local ethics commission of the Medical school.

Statistical evaluation of obtained values was performed by unpaired student's t-test. The level of significance was accepted at  $p < 0.05$ .

## RESULTS

An atherogenic lipoprotein profile, phenotype B, was identified in a subgroup of 50 stroke subjects (89.3%) and six stroke subjects had a non-atherogenic lipoprotein profile, phenotype A (10.7%) (Table 1).

Table 2 shows obtained lipid, lipoprotein values and the score for anti-atherogenic risk (SAAR) in the examined groups. The group of stroke subjects had increased values of cholesterol, triglycerides, and VLDL cholesterol ( $p < 0.0001$ ). Patients with stroke typically more often have hypertriglyceridemia (71%), compared to hypercholesterolemia, which was found in 25 subjects, and represented 44.6% of the stroke subjects.

The LDL1 subfraction in the stroke group was significantly decreased ( $p < 0.002$ ), and LDL2, together with strong atherogenic LDL3–7 subfractions, were higher, with high statistical significance ( $p < 0.0001$ ), compared to the control group. LDL 3–7 formed in the stroke group at ten times higher the concentrations than in the control group.

In addition, the score for anti-atherogenic risk (SAAR) was significantly higher ( $p < 0.0001$ ) in stroke group, compared to the control group.

The lipid result found in the arterial hypertension group could reflect a precondition that encompasses a particular vascular-metabolic constellation, with the serum concentrations close those of the stroke patient group. However, the lipid results of the stroke patients were higher.

**Tab. 3.** Atherogenicity of small dense LDL (Bernais & Krauss 2002; Packard 2003).

<b>Small dense LDL are highly atherogenic for:</b>	
*	low recognition by LDL-receptors (configuration alterations Apo B) →
*	enhanced aptitude for oxidation and acetylation →
*	Oxid-LDL → release of pro-inflammatory cytokines → muscle cell apoptosis
*	Oxid-LDL → release of metalloproteinase → collagen degradation
*	Oxid-LDL → enhanced aptitude for trapping by macrophages (scavenger-receptors) → stimulation of foam cell formation
*	easier penetration into the subendothelial space and formation of cholesterol deposits

## DISCUSSION

Dyslipidemia represents a risk factor for the development of cardiovascular disease and thus dyslipidemia has been classified as an atherogenic phenomenon. The goal of treatment of hyperlipoproteinemia, i.e. of dyslipoproteinemia, is to reduce the lipid concentration in serum to established target values of lipids (total cholesterol and triglycerides), but, the primary goal is to reduce the atherogenic potential of serum lipids (Backers 2005; Fruchart *et al.* 2008; Rubins *et al.* 2011). Dyslipoproteinemia is also one of the key phenomena in the pathogenesis of the onset of degenerative atherosclerotic alterations in brain vessels (Chun *et al.* 2009). The consequences of these alterations is stroke. Accompanied by high cholesterol levels, already declared a classic risk factor for the development of cardiovascular diseases, an increased concentration of triglycerides (TG) in serum can also play an important role in atherogenesis (Amarenco *et al.* 2008, Tanne *et al.* 2001). In our study, there was an increased serum TG-concentration ( $p < 0.0001$ ) compared to the controls, a pathological increase in the lipoprotein fraction VLDL ( $p < 0.0001$ ), and also an increase in all lipoprotein fractions, which are in a direct metabolic relation to the products of VLDL degradation: VLDL remnants i.e. IDL1–3 and all LDL lipoprotein family as well. The total LDL concentration was significantly increased, which was reflected by significantly increased LDL2 and LDL3–7 subfractions (both parameters  $p < 0.0001$ ). The LDL3–7 subfractions, i.e. small dense LDL, represent strong atherogenic lipoproteins in the serum of examined subjects.

Our results are in accordance with the results of clinical studies, which found, that an increased concentration of TG, together with low HDL levels, represents an independent risk factor for an ischemic cerebral-vascular event (Amarenco *et al.* 2008, Tanne *et al.* 2001). A decrease in triglyceride concentration through hypolipidemic treatment with statins or fibrates, reduces the risk of onset of a cerebral-vascular event up to 31% (Tanne *et al.* 2001, Rubins *et al.* 2001). The positive effect of treatment by fibrates (gemfibrosil) was confirmed after six months of treatment, however, the positive effect of treatment with statins was confirmed after a treatment period of 3–3.5 years. (Fruchart *et al.* 2008, Vrablik 2009).

The atherogenic lipoprotein spectrum, which plays a predominant role in the lipoprotein spectrum of stroke patients, is usually accompanied by a low serum HDL concentration, which we also confirmed in our stroke study. The combination of hypercholesterolemia, hypertriglyceridemia with a high concentration of small dense LDL, and a low concentration of HDL create a “murderous quartet”.

It should be emphasized, that reduced LDL1 in the lipoprotein spectrum of stroke patients, which was confirmed in this study, can definitively confirm the

### non-atherogenic character of this LDL1 subfraction.

A decreased LDL1 concentration in stroke patients, compared to the controls, does not evidently contribute to the atherogenic lipoprotein spectrum, found in the group of stroke subjects. This fact was also confirmed in other cardiovascular diseases, as such as ischemic heart disease, peripheral arterial disease and arterial hypertension (Oravec *et al.* 2010a, 2010b, Oravec *et al.* 2011).

An innovative laboratory diagnostic method to detect and characterize lipoprotein metabolism disturbances, a lipoprotein electrophoresis on polyacrylamide gel (PAG), the Lipoprint LDL system (Hoefner *et al.* 2001), can identify and quantify atherogenic lipoproteins in the lipoprotein profile of examined individuals (Oravec 2006; 2007a). This method can evaluate a lipoprotein profile, identify the atherogenic lipoprotein phenotype B, and the non-atherogenic lipoprotein phenotype A, based on the presence of a majority of non-atherogenic, or atherogenic lipoproteins in the lipoprotein profile of examined individuals (Van *et al.* 2007). An atherogenic lipoprotein profile is characterized by a rich presence of atherogenic lipoproteins, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL1–3), and, especially, by the presence of small dense low density lipoproteins (sdLDL), which form LDL3–7 subfractions and which are strongly atherogenic. Their strong atherogenic potential is a consequence of their chemical composition and biological characteristics (Table 2) (Berneis & Krauss 2002; Packard 2003).

The score for anti-atherogenic risk (SAAR), a relative value, is a newly introduced parameter. It determines the degree of the anti-atherogenic risk of the examined subject and is calculated as a ratio of non-atherogenic to atherogenic plasma lipoproteins (Oravec 2007a; Oravec 2007b; Oravec 2010). The calculated value reflects the risk degree of the examined individual, who is at-risk for a premature cardiovascular event. The SAAR correlates well with the phenotype of the lipoprotein profile, created by the Lipoprint LDL system.

Purely to obtain further knowledge, we also compared the lipid and lipoprotein concentrations of the stroke patient group to the lipid and lipoprotein concentrations in a group of newly diagnosed essential hypertension patients. The results found in the arterial hypertension group could reflect a precondition that encompasses a particular vascular-metabolic constellation, which subsequently continues to the onset of an acute stroke, when the serum lipid levels of cholesterol and triglycerides (and atherogenic lipoprotein entities) rise.

Stroke prevention is reasonable and hopeful only with a multifaceted approach to the polymorbidity of subjects (prevention and treatment of arterial hypertension, treatment of obesity and metabolic disturbances, and treatment of dyslipoproteinemia, diabetes and hypothyroidism) (Backers 2005; Bulas 2006; Rubins *et al.* 2011; Vrablik 2009). Fibrates are recommended for

the treatment of hyperlipidemia, which simultaneously reduce both increased triglycerides and cholesterol levels. Fibrates also reduce the formation of small dense LDL. Particularly recommended are the phenofibrates (Lipanthyl Supra 160, Lipanthyl Supra 215) to address the specific dyslipidemia issues.

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