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Serum Lipids and Statin Treatment During Acute Stroke

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1. Introduction

Epidemiological studies have shown a direct correlation between total serum cholesterol level and the risk of coronary disease. The significance of lowering serum total cholesterol (TC) and low density lipoprotein (LDL-C) and increasing high density level cholesterol (HDL-C) has been shown in various kinds of these studies on stroke; even on ones concerning cardiovascular events. The relative cardiovascular risk reduction by lowering the LDL-C ranges around 20-30%. The cardiac benefit of controlling serum lipid levels is specific among patients with evidence of chronic heart disease. Among the population without previous coronary disease, the primary preventive effect is less clear.

In acute stroke, the behavior of lipids changes from day to day and even up to weeks. The exact behavior of lipids is not ultimately that clear and even though this issue is very old, the studies about it are very sparse and not up-to-date. On the other hand, it is known that the specific biological effect of lowering lipids in cardiovascular and cerebrovascular conditions by using HMG-C_oA reductase inhibitors (statins) causes a modulatory influence on the myocardial, vasculoprotective and neuroprotective areas of the brain. Some of the beneficial effects of the statins may be secondary to the "class effect" or due to the individual characteristics of each drug. An example of this is seen, when under the use of statins, there is a 1.8% reduction of body weight with a 5-7% reduction in serum LDL-C. The coronary beneficial preventive effect was shown with pravastatin in the West Scotland Coronary Prevention Study (WSCPS), with lovastatin in the Air Force coronary Atherosclerosis Prevention Study (AFCAPS), with atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Study Trial (ASCOT-LLA) and with rosuvastatin in the Jupiter Study. All aspects of statin treatment during the acute stroke phases have not yet been clarified and what is known will be discussed in this chapter.

2. Lipids during acute stroke

2.1 Serum lipid levels during acute stroke

Since the end of the 60's, various articles have been published concerning the lipid level of stroke patients. Most studies of the studies analyzed the levels for weeks or months after stroke. However, none of these studies examined the lipid profile during the stroke event. In 1987, Mendez et al. [1987] studied 22 consecutive patients in three different time points, within 24 hours of stroke and 7 days and 3 months later. The mean level of total cholesterol

(225 ± 15 mg/dl) decreased to a lower level (189 ± 19 mg/dl) after 7 days and increased again to a higher level (247 mg/dl) after 3 months (significance of $p<0.05$). In transient ischemic attack patients (TIA), the profile was similar, but did not reach the level on admission at 3 months. The levels of total cholesterol were especially high among younger patients significantly. The profile of very low density lipoproteins (VLDL) was a similar one (16 ± 6 mg/dl, 13 ± 4 mg/dl, 16.5 ± 5, respectively to the time points). There was a correlation between serum levels, group of age and severity of strokes with the triglycerides (186 ± 45 mg/dl, 173 ± 36 mg/dl, 209 ± 43mg/dl., respectively), and on the low density lipoprotein (LDL) (186 ± 17 mg/dl, 149 ± 0.5 mg/dl, 202 ±19mg/dl., respectively). High density lipoprotein (HDL) showed a reciprocal profile (23 ± 3.0 mg/dl, 27 ± 4.5 mg/dl, 29 ± 4.0 mg/dl., respectively). The levels were higher in aged patients and in TIA ones. The differences in most of the tests had not reached statistical significance.

Woo et al. [1990] analyzed data of 171 patients during acute ischemic stroke (48 hours and 3 months later). They found a high level of total cholesterol in the early stage of acute stroke (221 ± 46 mg/dl vs 205 ± 50 mg/dl, $p<0.0001$) and of LDL-C (147 ± 43 mg/dl vs 135 ± 46 mg/dl, $p=0.05$). Triglycerides were lower on admission and non significant (133 ± 1.0 mg/dl vs 151 ± 89 mg/dl, $p<0.0001$).No changes were found in HDL and VLDL. There was a significant correlation toward better outcome in the higher level of total cholesterol, triglycerides, VLDL and HDL and reciprocal concerning HDL. The levels were lower in lacunar infarction patients. A significant finding was shown in lacunar infarction and was only higher in total cholesterol and LDL-C during the first 48 hours.

In 1996 Aull et al. [1996] examined the data of 37 patients with TIAs or minor strokes, during the first 24-48 hours and compared the data to the results of other patients after 49-168 hours. In spite of the severe limitations of the design of the study, they found a higher level of total cholesterol in the 24-48 hour group (231.7 ± 42.8 mg/dl vs 192.2 ± 36.0 mg/dl, $p<0.05$). There was no difference concerning the triglyceride and HDL-C levels.

A study which analyzed the post ischemic stroke cholesterol and LDL-C levels in various time points – on admission; day 2 and 3; week 1, 2 3 and 4; although in only 19 patients, was published by Kargman et al. [1998] based on the data from the Northern Manhattan study (NOMIS). They found a similar profile for cholesterol and LDL-C. The highest level was on admission, decreased to a lower level on the second day, reaching the lowest level after 1 week, and a recurrent increase on the 4th week, without reaching the original level on admission (cholesterol - 295 ± 57.6 mg/dl, 214 ± 53.2 mg/dl, 215 ± 58.2 mg/dl, 208 ± 43.5 mg/dl, 213 ± 45.3 mg/dl, 213 ± 45.3 mg/dl, 218 ± 47.9 mg/dl and 216 ± 55.8 mg/dl; LDL - 154 ± 56.0 mg/dl, 137 ± 52.1 mg/dl, 133 ± 49.4 mg/dl, 124 ± 39.2 mg/dl, 131 ± 36.6 mg/dl, 133 ± 43.3 mg/dl, 130 ± 45.6 mg/dl). The profile of triglycerides showed the lowest level on admission (181 ± 94.7 mg/dl) and a maximal level after the first week (250 ± 151.6 mg/dl). HDL-C did not show any dynamic values.

2.2 Level of lipids during acute stroke as a prognostic marker for outcome and death

Some studies analyzed the level of lipids during the acute state of stroke as a prognostic marker for the later outcome.

2.2.1 Total cholesterol

Vauthey et al. [2000] analyzed the data base of 3,273 consecutive patients with first ever stroke. They found a high mortality rate ($p=0.002$) and a poorer one month outcome ($p<0.01$) in correlation with low levels of total cholesterol. The association between low serum level of total cholesterol and worse outcome as well as with mortality rate was

described also by Dyker et al. in 977 patients [1997] and by Olsen et al. [2007] when measuring the total cholesterol in 513 patients within 24 hour time window. The neurological score used for evaluation was the Scandinavian Stroke Score (SSS). Li et al. [2008] in a prospective observational study of 649 patients, including all types of stroke and intracerebral hemorrhage patients also found a high level of correlation of $p<0.005$ between low levels of total cholesterol and better 90 day outcome, using the Scandinavian Stroke Score (SSS). The correlation between high level of serum total cholesterol and better outcome was confirmed during follow-up post stroke. Simundic et al. [2008] demonstrated these findings also in their acute stroke study which included 70 patients. Pan et al. [2008] examined the functional Barthel Index Scale in 109 patients in different stages of outcome at 2 weeks and 1, 2, 4 and 6 month and confirmed this observation in each of the examination points. E. Cuadrado-Godia et al. [2009] found this association in both sexes, but also more prominently among the male. In their study, which included 591 patients, a neurological score (NIH Stroke Scale), as well as a handicap score (Modified Rankin Scale – mRS) were used. A sex dependency was found not only in the higher levels, but also in the lipid level as outcome prognostic markers. The level of total cholesterol was higher among females (187.7 ± 45.0 mg/dl vs 176.7 ± 43.8 mg/dl, $p=0.005$). The association between high level of total cholesterol and better outcome was highly significant among males and not among females ($p=0.0014$). This study included naïve and non naïve statin users, as well as patients under tPA administration. The overall lipid level was relatively low (6% total cholesterol and >250 mg/dl). Contrary to these results, von Budingen et al. [2008] in Switzerland analyzed prospectively collected data of 899 patients. Each of them neurologically scored using the NIHSS scale. The authors compared the scores on admission and day 90 and found no correlation between neurological recovery and cholesterol level.

2.2.2 High density lipoprotein (HDL) level

The HDL levels during acute stroke were analyzed as part of the lipid examination in Li et al. [2008] in 649 patients and a high correlation ($p<0.001$) was found between low HDL and severity of stroke after 90 days. Sacco et al. [2001] in a population based incident case controlled study, which included 539 patients with first ever ischemic stroke, evaluated a protective effect of high HDL-C (> 35mg/dl). The association between HDL-C level and better outcome more was significant in the serum level group of 35-39 mg/dl and as most effective in the patient group having HDL-C > 50 mg/dl. The study was designed for the elderly population (>75 years) of all ethnic groups. The previously mentioned study of Cuadrado-Godia et al. [2009] found the same tendency of higher HDL among females (52.9 ± 15.1 mg/dl vs 45.1 ± 13.4 mg/dl) and an isolated effect toward better outcome in association with higher HDL levels only among males ($p<0.001$). There was the same tendency in the total cholesterol/HDL ratio showing higher a ratio among males (3.7 ± 1.2 mg/dl vs 4.11 ± 1.4 mg/dl, $p=0.002$). A sex dependency was shown also by Russman et al. [2009]. A higher level among females (42.5 mg/dl vs 34.2 mg/dl, $p=0.05$) was demonstrated, as well as being less prone to stroke and having a better outcome (mRS $p=0.059$). It was assumed as the increase of HDL-C among females was dependent on the higher endogenous estrogen regulation APO AI [Hamalainen et al., 1986; Longcope et al., 1990].

2.2.3 Triglycerides (TG)

The association between the level of TG and outcome is more controversial. Whereas, most studies showed a correlation between high level and better outcome and recovery [Li et al.,

2008], other studies had not found a correlation or a tendency, and their results not reaching statistical significance [Simundic et al., 2008].
In summation, all studies confirmed the finding of direct, independent correlation between higher total cholesterol level, during acute stroke, and HDL-C and better outcome and recovery. This tendency was shown especially among the elderly population in different races and ethnicities. Some studies, in which the results were not absolutely clear, showed that a high triglycerol level has a tendency toward better outcome. A higher level was expected among females, and among males, the elevation of lipids in serum, and especially in total cholesterol and HDL, are of more importance as better outcome markers.

2.3 Lipid profile and outcome after thrombolysis in acute stroke

Intravenous administration of tissue plasminogen activator (tPA) is an improved tool for better outcome in a large group of acute ischemic stroke. The main severe complication of tPA is secondary bleeding after the administration of the drug. The association of lipid and tPA was examined in severe strokes and revealed controversial data. In a retrospective study, which included tPA treated patients, intraarterial thrombolysis on mechanical embolectomy found an association between secondary hemorrhagic transformation and LDL cholesterol level. Bang et al. [2007] examined 104 patients checking parameters for tPA outcome in intravenously treated patients. They found that low LDL (odds ratio (OR) 0.968 per 1 mg/dl) increases independently upon static treatment has a high risk for hemorrhagic transformation. Uyttenboogaart et al. [2008] one year later found controversial findings. They found no association between LDL, HDL and total cholesterol levels and usage of statins as predictive factors for secondary bleeding. On the other hand, they demonstrated a significant independent correlation between high levels of triglycerides and the risk of secondary bleeding, but not with unfavorable outcome in a three month analysis (p=0.53). Among 252 patients, they found that the mean triglyceride levels were significantly higher among secondary bleeding patients (2.5 mmol/L vs 1.8 mmol/L, p=0.02) and reaches statistical significance, p=0.01, as an independent associated factor. The difference in HDL level (1.0 mmol/L vs 1.2 mmol/L, p=0.03) did not reach statistical independent significance. Ribo et al. [2004] investigated low Lp(a), as an isolated marker for hemorrhagic transformation in tPA treatment, but found no association.

2.4 Lipid and hemorrhagic transformation during acute ischemic stroke

Most studies showed an association between low level of cholesterol and triglycerides and intracerebral bleeding. This assumption is controversial. Kim et al. [2009] analyzed 377 patients of different types of stroke to investigate the association between serum lipids and hemorrhagic transformation. Lipid profile was evaluated on admission (< 24 hours) and MRI done within 1 week after stroke. They found a difference between large artery artheromathosis and cardioembolic origin. In large atheromatotic patients, a low level of LDLC was significantly independently correlated with bleeding (OR 0.46/1mmol/L increase, p=0.004); in the lowest quartile (≤ 25 percentile) and the OR was 0.21 (p=0.001). The low level of cholesterol (lower quartile OR 0.63 for 1 mmol/L increase, p=0.02) was possibly associated with transformation into bleeding. No association at all was found in the cardioembolic group. The association between low total cholesterol and LDL-C is not yet established. Endothelial damage, blood extravasation around microvessels and the direct effect on blood brain barrier were discussed. A correlation between lipids and bleeding was

shown by Ramirez-Moreno, who analyzed the data of 88 intracerebral patients. There was no correlation between low LDL-C level and death [Ramirez-Moreno et al., 2009].

2.5 Conclusion

The consensus is that total cholesterol in the LDL form decreases during acute stroke. As for VLDL and HDL, the acceptable consensus is that the serum level of lipids is irrelevant for estimation of the basic outcome of the individual, up to at least 7 days from the event. To estimate the real lipid level, it is best to wait for 30 days. It is also accepted that lower level of total cholesterol and LDL are predictor factors for a worse outcome, especially in larger cortical infarction strokes. However, the studies concerning this consensus are considered poor and include only a limited number of patients. This consensual date is also responsible for the examination of serum lipids only after a month in most of the acute stroke status studies. The very large data base of the various placebo groups of the disease of the diverse acute stroke studies, including ones on neuroprotection studies and a thrombolytic trial are not involved with lipid profile at the acute and hyperacute phases. It is also assumed that studying the subgroups of patients involving race, ethnicity, disease coexistence, various medication usage and various origins of the stroke were also neglected. A better clarification of such subgroups may be of importance for understanding the pathogenesis and clinical and therapeutic aspects in the proper care of stroke victims.

2.6 Lipoprotein and APO Lipoprotein (APO Lp) in acute stroke

Lipoprotein (a) was first described by Berg et al. in 1963. It was defined as a genetic variance of β lipoprotein and was inherited in an autosomal dominant form. The Lp(a) is a LDL-like molecule, consisting of Apo(a) which is linked by a disulphide bridge to apolipoprotein B100. Lp(a) is evaluatory being specific to humans and primates. The sequencing of Lp(a) at the protein and DNA levels has a high degree of similarity to plasminogen, leading to cross reactivity between both. A lower degree of similarity can be found with other "kringel" loop proteins, such as prothrombin, factor XII, and macrophage stimulating factor. The similarity is responsible for the endothelial cell fibrinolysis and the indication of procoagulant state.

The Apo(a) gene is highly polymorphic and more than 35 different sized alleles (ranging from 187-648 kDa) have been identified. The size of polymorphismus of Apo (a) is mostly dependent upon the genetically determined number of kringel IX type 2 repeats.

A few small studies have analyzed the quantitative profiles of Lp, APO Lp (a), and APO Lp(b) alongside the time axis after acute stroke. In the early 90s, Woo et al. [1990] discussed this topic. He examined APO Lp A_1 and APO B levels in 171 patients during the first 48 hours and 3 months later. During the acute phase, the APO Lp A_1 level was higher overall in all stroke subjects, as well as in cortical ischemic stroke and intracerebral bleeding, but not in lacunar stroke. The increase was in the range of 8-10%, but did not reach statistical significance (122.0 ± 30.9 vs 117.4 ± 26.4 mg/dl; 121.2 ± 31.8 vs 115.6 ± 26.4 mg/dl; 127.5 ± 34.7 vs 117.2 ± 29.8 mg/dl; and 119.1 ± 26.8 vs 119.1 ± 23.8 mg/dl; respectively).

The level of APO B showed a similar tendency; however, the increase of APO B level reached statistical significance among the cortical subgroup ($p<0.008$) (95.6 ± 27.9 vs 87.1 ± 23.4 mg/dl; 98.0 ± 26.5 vs 89.5 ± 27.4 mg/dl; 90.5 ± 25.3 vs 83.9 ± 22.2 mg/dl; and 98.7 ± 32.9 vs 86.9 ± 32.9 mg/dl; respectively). The Lp(a) showed reciprocal behavior. There was a decrease of Lp (a) during the acute phase (among 10-15%), significantly in cortical stroke, but not in intracerebral bleeding. The level of Lp(a) after three months of stroke was

significantly high in cortical infarct also in other studies [Yingdong & Xiuling, 1999]. These studies were contradictory with another study which involved 127 patients, having not found any difference between the acute stage level and recovery stage [Misirli, 2002].
The NMSS (North Manhattan Stroke Study) at the end of the 90s, Lp (a), APO AI and APO B were examined during the acute state of 24 hours and in the follow-up stages at 2 and 3 days and weeks 2, 3 and 4. Nineteen subjects fulfilled all the criteria, mean age was 65.0 ± 12 years and all types of ischemic infarcts were included. The Lp (a) concentration was elevated (52.0 ± 28.6 mg/dl) on admission (<24 hours) and remained (>30 mg/dl) in 15 patients after 1 month. The Lp(a) level began to decrease (46.0 ± 25.8) on day 3 and remained constant up to the 4th week (43.0 ± 29.7 mg/dl). The data did not reach statistical significance.
The APO AI level did not show any significant changes (day 1 130.0 ± 26.4 mg/dl; day 3 128.0 ± 27.1 mg/dl; 4th week128.0 ± 28.3 mg/dl). The APO B showed an increased level at the acute stage (141.0 ± 46.1 mg/dl), decreased at day 3 (131.0 ± 41.5 mg/dl) and remained stable up to the 4th week (132.0 ± 37.2 mg/dl). Another study, which analyzed the data of 31 cerebral hemorrhage patients and 10 ischemic strokes, found a decrease of APO A in the intracerebral patient group up to the 14th day. Lp(a) levels increased simultaneously up to the 7th day. In the ischemic group, APO A decreased, whereas no change was observed in the APO B and Lp(a) levels.
At the end of the 90's, Seki et al. [1997] analyzed the level of Lp(a) in association with thrombomodulin and total cholesterol levels in 28 cerebral thrombus patients during the acute phase of cerebral thromboses. The examination took place up to three days after the event. The event included large vessel thrombosis in lacunar infarction. The data was compared with 36 patients who had chronic phase cerebral thrombosis (> 1 month post event), 6 patients with chronic post intracerebral hemorrhage (> 3 months post event) and a control group of 37 volunteers. The plasma level of Lp(a) was significantly higher in the acute stage of cortical strokes (24.2 ± 20.9 mg/dl in cortical strokes; 13.4 ± 8.6 mg/dl in lacunar strokes; 24.2 ± 20.9 mg/dl in cortical strokes; and 11.6 ± 8.0 in controls; $p<0.0001$. significant higher level was found also in recurrent strokes (19.8 ± 17.6 mg/dl, $p<0.05$). Higher levels were demonstrated also in chronic post stroke phases (16.9 ± 14.7 mg/dl after 1 months), but not in bleeding ones after 3 months. The total cholesterol levels were low as expected. Van Kooten et al. [1996] in a cross sectional study which included 151 consecutive patients found a higher level of Lp(a) in 355 of stroke patients. The media values were 191 (12-1539) mg/dl in stroke and 197 (10-1255) mg/dl among transient ischemic stroke patients. In intracerebral hemorrhage, an elevation of Lp(a) to 153 (11-920) mg/dl was also found. Although the level of Lp(a) was increased in about one third of acute stroke patients, it was not characteristic of a stroke profile or outcome progress. These are contradictory to other studies having found only independent correlation between Lp (a) level and acute stroke [Misirli et al., 2007].

2.6.1 Summary

The data is inconclusive and is based on small group studies. Most of the studies indicate mild increase of APO AI and APO B in the acute stage after infarction lasting up to three days and returning to normal values after weeks or months. The data regarding Lp(a) is controversial. It seems that in cortical infarction the changes are more predominant, but in cerebral bleeding, only some of the changes may be present. The difference in results can be explained by the use of a very small patient sample, differences in laboratory techniques and homogeneity in patient populations.

2.7 Oxidized Low Density Lipoprotein ($_{ox}$LDL)

LDL particles can be modified into a form defined as oxidized LDL ($_{ox}$LDL). It is a proatherogenic and proinflammatory mediator induced by the inflammatory stimuli and the presence of oxygen enzymes (ROS), especially myeloperoxidase and nitric oxide synthase (NOS). $_{ox}$LDL looses the affinity to bind to LDL receptors and gains an affinity to bind to the protein receptor family called scavenger receptors. Their subfamily A is present on macrophages, platelets and other cells and has the affinity to bind and internalize the $_{ox}$LDL particles and other cells; plus, to gather up the cholesterol in the cells and create foam cells. This multi-functional membrane receptor shares also an effect on apoptotic cells and microbial agents.

An important scavenger type is CD 36, which has a concrete affect on $_{ox}$LDL. The signaling pathways include activation of SCR family kinase, MAP kinase, and the Vav family of quinine nucleotide exchange factors. The CD 36 deficient animal models show inhibition of thrombus formation, reduction of accumulation of microparticles and inhibition of foam cell creation. The scavenger receptor B type I (SR-R_1) plays a main role in mediating cholesterol exchange between cells and diverse lipoproteins. HDL-SR-R_1 is atheroprotective, cardioprotective and vascular protective by a direct endothelial affect on the kinase pathways. This includes plasma membrane cholesterol flux, requiring the C termination of the PDZ domain on the receptor and mediation of the membrane cholesterol binding; it includes also the upregularion of nitric oxide production.

In astrocytes surrounding the tissue of infarcts, an activity of $_{ox}$LDL was shown stimulating interleukin 6 secretion, active initiation of immunity and tissue survival [Shie et al., 2004]. The behavior of $_{ox}$LDL during acute stroke is characterized by a significant increase of its level immediately after onset of infarction, lasting up to three to seven days. Uno et al. [2003] compared the plasma level of $_{ox}$LDL in 45 patients after acute ischemic stroke and in 11 patients with intracerebral bleeding and compared it to a control group. They found a highly significant correlation ($p<0.0001$) between high level of $_{ox}$LDL and only cortical ischemic stroke. The mean values in the three groups (ischemic stroke, hemorrhagic stroke and controls) resulted in the following outcomes: 0.245 ± 0.22 vs 0.13 ± 0.007 and 0.179 ± 0.0232 ng/microg $_{ox}$LDL.

A second study of the same group [Uno et al., 2005] compared the $_{ox}$LDL of 44 patients with the imaging data DWI-PWI (diffusion perfusion weighted index) mismatched. The results showed a statistical correlation between enlargement of the ischemic phase and the serum elevation of $_{ox}$LDL. The correlation was specific for cortical infarcts and not for subcortical strokes or for huge hemispheric infarctions. The first blood sample was examined during the first 24 hours after infarction. The elevation profile showed a high level up to seven days and normalization of serum level up to 14-30 days post stroke.

Another study compared $_{ox}$LDL in 28 patients after acute atherothrombotic and lacunar infarction. There were significant ($p<0.001$) higher serum $_{ox}$LDL level in atherothrombotic strokes compared with the small vessel disease and control groups. The values were as follows: 106.85 ± 11.6 U/L; 81.0 ± 28.2 U/L; and 79.1 ± 20.4 U/L; respectively. The rationale for the elevation of the $_{ox}$LDL during acute stroke was due to the acute increase of oxidative stress and induction of the adhesion molecules.

3. Statins during acute stroke

3.1 Statins

Statins are competitive inhibitors of the enzyme HMG (3-hydroxy 2 – methylglutaryl) C_OA reductase. This enzyme is considered to have the most important role for limiting

cholesterol biosynthesis. The statin effect is based on the capacity of its binding to the active site of the HMG C_oA reductase. Statins reduce the intrahepatic cholestasis amount, increase the LDL receptor turnover and reduces the VDLD production by acting on the hepatic APO B secretion and reduction of the plasma triglycerides level. It also acts on the clearance of VLDL.

Six main statins are now on the market – lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin and rosuvastatine. Although all statins share the same "class effect", there are predominant differences among the various types of statin drugs. The non selective reduction of the LDL substances, especially the small, dense LDL particles, is more specific for atorvastatin and rosuvastatin. The effect of increasing HDL-C in serum and the apo lipoprotein AI is typical for simvastatin and rosuvastatin. Rosuvastatin and atorvastatin are also very effective in the dynamic changes of serum triglycerides, although the individual effect of these diverse statins and the drug's is very different from person to person, often dependent upon race and genetic ethic differences [Mangravite et al., 2008; Mangravite & Krauss; Puccetti et al., 2007].

The benefit of statins in primary and secondary prevention of coronary heart disease and the formation of atherosclerotic plaques is well established [Sandowitz et al., 2010a, 2010b]. The effect of statins on the cerebrovascular system and the brain tissue is based on their pleiotrophic effect beyond the direct lipid effect. The vasoeffective action is based on a direct upregulation of the endothelial nitric oxide synthase (eNOS), increase of the bioavialability of NO 20-22 [Ito et al., 2010; Laufs et al., 2000; Nakata et al., 2007; Yagi et al., 2010; Ye et al., 2008;] and inhibition of NADPH oxidase [Antoniades et al., 2010; Rueckschloss et al., 2001]. This vascular effect precedes the lipid one. The decrease of the asymmetric dimethylarginine (ADMA) [Nishiyama et al., 2011] stabilizes the blood barrier integrity [Sierra et al., 2011], acts on the apoptotic pathway [Carloni et al., 2006] and stimulates excitatory Neurotransmitters are other targets of the statin effects concerning its action on the vascular system and cerebrovascular event.

3.2 Statins in stroke

Statins have multiple targets of action in stroke. The main confirmed activity is in the vasculature reactivity action on the eNOS and NO and by action on the inflammatory pathways. The effect was shown in animal model studies. In human ones, it was shown that statin pretreatment has a favorable effect on outcome. The issue of initiation of statin treatment during acute stroke is not yet resolved. There are indications that the efficacy may be dependent upon type of statins and that this effect is an individual and not a "class effect". The multiple mechanisms of statins on ischemic brains are based on the different targets of action. Statins increase eNOS [Ito et al., 2010; Ye et al., 2008] and reduce activity of nicotinamide adenine dinucleotide phosphate oxidase and decrease endothelin 1 and 2 and the expression of AT_1 receptor [Yagi et al., 2010]. It also acts on the inflammatory system by decreasing the nkFB [Nakata et al., 2007; Ye et al., 2008] and the expression of interleukin (IL) 1p, IL6 and MCP. It also has an increasing effect on expression of tPA and a decreasing effect on plasminogen activator inhibitor 1. Additional targets of action are on the reactive oxygen species, the metalloproteinase 9 and blood brain barrier and on platelet activity [Sierra et al., 2011]. Also, various animal model studies demonstrated improvement in outcome by induced stroke on different types of models and administration of statins (mostly simvastatin or atorvastatin).

3.3 Acute stroke in patients under statin treatment

The issue of mortality and functional outcome after ischemic stroke in patients under statin treatment was analyzed in different prospective and retrospective studies. As inclusion criteria for all the studies, statins were defined as such without characterization of the type of statins. The results of those studies was based on the assumption of a statin "class effect" for neuroprotection and as a lipid lowering agents. The data of preclinical animal model studies [Berger et al., 2008; Bosel et al., 2005; Carloni et al., 2006; Domoki et al., 2010; Franke et al., 2007; Lee et al., 2008; Moonis et al., 2005; Sironi et al., 2003; Yrjanheikki et al., 2005] have indicated a different neuroprotective effect of the various types of statins and raises the fact that all these results must be taken into consideration.

Marti-Fabregas et al. [2004] in a prospective study, which included 167 patients, found a favorable outcome after three months post stroke and on statin pretreated patients compared with the untreated group (80% vs 51.8%, p=0.059) using handicapped mRS scores. Using functional disability Barthel Index (BI) scoring, similar results were found. Yoon et al. [2004] examined 436 patients with ischemic stroke. He found a good outcome (defined as mRS score >2) in 52% in the statin protected group, compared with 38% among controls (p=0.02). At the same time, Greisenegger et al. [2004] confirmed the findings with a cross-sectional study of 1,691 patients. They found also, that among the diabetes mellitus patients, the percentage of bad outcome (defined as mRS score of 5-6) was 16% of the untreated patient group, whereas no bad outcome was found among the statin treated group.

One year later, Moonis et al. [2005] compared 129 patients under previous statin treatment with a group of 600 untreated patients. The pretreated patient group had a significant better outcome at 12 weeks, using NIHSS (p=0.002) and mRS scoring (p=0.033).

In January 2008, Reeves et al. in Michigan analyzed the data of the Paul Coverdell National Acute Stroke Registry. They data included 1,360 ischemic stroke patients in 15 hospitals. They also confirmed the previous studies. In this study, the patients under statins were associated with lower odds of poor outcome. There was also a significant difference among race. Whereas, the odds ratio among Caucasian Americans was significantly toward better outcome from the statin treated group (OR=0.61), the odds ratio among Afro Americans was non significant (OR=1.82).

The north Dublin Population Stroke Study [Ni et al., 2011] was a population based prospective cohort one and included 448 ischemic stroke patients with 305 (134 patients) being pretreated with statins. The most common prescribed statins were atorvastatin (70.2%) and pravastatin (24.6%). NIHSS and the mRS scores were compared with 112 patients of the untreated group and 189 newly post stroke statin treated group. The odds ratio of the pretreated group in comparison to the untreated group was 0.04 (CI 0.0-0.33, p=0.003) at 7 days, 0.23 (CI 0.09-058, p=0.002) at 90 days and 0.48 (CI 0.23-1.01, p=0.05) at 1 year. The newly acute post statin group demonstrated similar results – lower OR (0.12, p=0.003) after 7 days, similar OR (0.16, p<0.001) after 90 days and better OR (0.26, p<0.001) after 1 year.

Arboix et al. [2010] collected date on 2,082 consecutive patients with first ever ischemic stroke incorporated from prospective hospital based stroke registry during 19 years. They found a better prognosis for pretreated patients concerning death (6.0% vs 11.5%, p=0.001), symptom-free (22% vs 17.5%, p=0.025) and severe bad functional outcome (6.6% vs 11.5%, p=0.002). Imaging studies confirmed the clinical data results. Stead et al. [2009] showed also

that among 508 patients with ideal LDL level (≤ 100 mg/dl) the functional outcome was significantly better among statin users (p<0.001) [Reeves et al., 2008]. The neuroprotective pleiotrophic effect was assumed to be the reason for this phenomenon. Nicholas et al. [2008] found a smaller volume of infarcts in statin pretreated patients (p=0.01). Ford et al.[2011] examined the reperfusion in acute ischemic stroke using MR scan within 4.5 hours and 6 hours. Twelve of the patients were statin pretreated and 19 were not. They found a significant better reperfusion among the treated group (50% vs 13%, respectively; p=0.014). The findings were in association with improvement of NIHSS scores after one month.

3.3.1 Summary

All trial data indicate a significantly better for pre users of statin in ischemic stroke. This finding included mortality rate, early and late handicap and functional outcomes, as well as Neuroimaging findings.

3.4 Satin treatment withdrawal during acute stroke

The assumption that sudden discontinuation of statins may have a critical effect on the body is based on its biological characteristics and observations within in vitro studies and in vivo animal models. These studies showed dramatic down regulation of eNOS expression and reduction of eNOS protection up to 90%. This process is dependent upon changes in Rho and Rac regulation and changes in activity of Rho kinase. Platelet factor 4 and thromboglobulin change as well. This significant involvement in the vascular endothelial biology may, as usual, have a rebound effect. There are studies showing almost complete disappearance of the statin protective effect in experimental acute stroke after discontinuation of the drug for two days [Chen et al., 2005; Karki et al., 2009]. Changes of cerebral blood flow, in the posterior circulate system, was observed as well [Berger et al., 2008; Xu et al., 2008]. In humans during a randomized controlled study, Blanco et al. [2007] examined the effect of discontinuation of atorvastatin 20 mg / day in cortical stroke patients' outcomes. Of 219 patients, 89 were pretreated with statins, 43 continued the study and 43 stopped for 3 days. The data analysis showed high percentage of bad outcome (mRS > 2) among discontinued patients (60% vs 39%, p=0.043); a worse early neurological outcome (day 4-7 using NIHSS score, p=0.002) and a significant larger volume of stroke (p<0.0001). In comparison of the patient group naïve to statins, the risk of worse early neurological outcome was 19.01 and the risk of larger infarcts was 13.51 in total. However, meta analysis of 18 studies, enrolling 14,303 patients after acute coronary syndrome and initiation of statins within 14 days following event did not find reduction of stroke, similar to all cause mortality and heart attacks in a period of a four month follow-up.

3.4.1 Summary

The preclinical experimental data raise the speculation of a serious 'rebound' effect by the discontinuance of statins towards a worse outcome. There are too few clinical studies confirming this hypothesis.

3.5 Satin in tissue Plasminogen Activator (tPA) ischemic stroke patients

The association between statin treatment and intracerebral hemorrhage, especially after publication of the results of the SPARCL study [Goldstein et al., 2008; Goldstein et al., 2009; Welch, 2009], raises the very genuine issue of the adverse event after tPA treatment.

3.5.1 Intravenous tPA (IVtPA)

Uyttenboogaart et al. [2008] analyzed the data of 252 patients treated with tPA. They found that high level of triglycerides and low level of HDL were independent risk factors for bleeding (p==0.02, p=0.03, respectively). However, there was no association between statins and 90 day outcome. Makihara et al. [2010] analyzed the data of the Japanese SAMURAI rtPA Registry and confirmed the well established fact that administration of IV tPA increases the risk of intracerebral hemorrhage, but increases also the rate of favorable outcome. The usage of statins did not influence any of these findings. Miedema et al. [2010] published the results of a prospective observational cohort study of 476 patients treated with IV tPA with 20% of the patients being on statins. They did not find any favorable effect for 90 days in functional and neurological outcome (OR 1.1, P=0.87). This tendency was consistent in all five groups of stroke subtypes according to the TOAST classification. On the other hand, no increase of bleeding was observed as well.

3.5.2 Intraarterial tPA

Meier et al. [2009] in a monocenter study of 311 consecutive patients, of whom 18% were statin pretreated, found a higher rate of intracerebral bleeding among statin users (OR 3.1, P=0.004). This fact was unrelated to the 90 day functional and neurological outcome. The group of statin users included atorvastatin (36.4%), pravastatin (36.4%) and simvastatin (unknown %) users. Restrepo et al. [2009] examined the impact of statins before and after intraarterial fibrinolysis and percutaneous mechanical embolectomy. The study was a single center one in Los Angeles. Statin use was related to a better outcome with decrease of 6.5 units in the NIHSS score after discharge (P=0.016). There was no increase in the post procedure bleeding.

3.5.3 Summary

The data of the statin effect on tPA is sparse. However, it seems that intravenous administration has no beneficial effect of a better outcome, but also no higher rates of secondary bleeding adverse events.

3.6 Onset of satin treatment during acute stroke

The pleiotropic neuro- and vasculoprotection effect is already described. Simvastatin, rosuvastatin, atorvastatin and pravastatin had been shown to have a neuroprotective effect in animal models. It has been shown that simvastatin reduces stroke volume in rats up to 50% and pravastatin reduces the cerebral post stroke edema [Mariucci et al., 2011]. The usage of an intravenous statin in stroke is based on the intravenous formulation of the hydrophile types of statins – rosuvastatin and pravastatin. Rosuvastatin in intraperitoneal administration in rats improved clinical outcome and infarct volume [Prinz et al., 2008]. In humans, the studies are few. According to the latest updated cholesterol management guidelines, it is recommended that anticholesterol treatment be performed immediately after stroke. In the North Dublin Study, 134 out of 445 patients (30.1%) had begun the treatment during the first 72 hours after admission and 7% were treated with atorvastatin and 24% with pravastatin. The early and late survival and outcome were significantly better compared with the no treated group and equivalent to the previous statin treated group. In the data of the FASTER study concerning the assessment of minor stroke and transient ischemic attacks (TIAs) to prevent early recurrency, the group of patients under simvastatin within 24 hours of onset showed an increase of absolute risk of 3.3% toward bad outcome

[Kennedy et al., 2007]. Montaner et al. [2008] performed a simvastatin placebo controlled study of 60 patients having cortical stroke and receiving simvastatin 3-12 hours after onset of symptoms and found significant improvement after 3 days (44.4% vs 17.9%, p=0.022), but also a higher, non significant rate of mortality (OR 2.4 CI 1.06-5.4).
A head-to-head study was performed by Lampl et al. [2010] and included 371 patients. The administration of statin was immediate comparing three elements - simvastatin and atorvastatin at 40mg/daily and 80 mg/daily. The statistical analysis indicated that the subjects receiving simvastatin had a highly significant worser outcome as noted by neurological (NIHSS score) and functional (mRS) measurements compared with the two dose atorvastatin treated patients ($p<0.001$). The scores of atorvastatin 80 mg were marginally better than those of atorvastatin 40 mg (p=0.08).

3.6.1 Summary

The complete picture of statins as neuroprotectors during the acute phase of stroke is not yet resolved. Very few studies have been performed. It is plausible to assume that the pleiotropic neuroprotective effect is an individual characteristic of each drug and not a part of a "class effect". Many more studies and positive data are needed to confirm this assumption.

3.7 Satin in acute subarachnoid hemorrhage

The rationality of administration of statins in subarachnoid hemorrhage is based on the fact that statins have an effect on eNO and eNOS, as well as an anti-inflammatory mechanism. Therefore, it is assumed that statins may have an anti-vasospastic effect. These hypotheses were confirmed in animal studies using simvastatin. There have been some meta analysis studies which calculated the effect of statins on subarachnoid hemorrhage. Sillberg et al. [2008] published one meta analysis in 2008. Most of the studies used simvastatin in dosages of 20 mg/d and 80 mg/d and pravastatin at 40 mg/d. Sillberg et al.'s [2008] meta analysis consisted of three randomized controlled trials and incorporated the studies of Lynch et al. [2005], Tseng et al. [2005] and Chou al. [2008]. The overall number of included patients was only 158. The authors found that the incidence of vasospasm (RR 0.75 CI 0.54-0.99), delayed ischemic deficits (RR 0.38 CI 0.17-0.83) and mortality (RR 0.22 CI 0.06-0.82) were significantly reduced in the statin treated group.
Vergouwen et al. [2009] published another metal analysis of 4 studies and included 190 patients. Two studies were about simvastatin and one about pravastatin. No beneficial effect concerning transcranial Doppler vasospasm, delayed cerebral ischemia, poor outcome or mortality was found.

3.7.1 Summary

Although preclinical and various single center studies have been very promising, a positive conclusion about the benefit of statins in subarachnoid hemorrhage has not yet been finalized.

3.8 Satin in acute intracerebral hemorrhage

Previous studies on animals showed a significant improvement of functional outcome after use of simvastatin or atorvastatin, as well as reduction of hematoma volume at four weeks (Karki). Enhancement of neuroprotection and neuroplasticity effects in rats was assumed.

In humans, some studies analyzing the outcome of intracerebral hemorrhage patients under statin treatment. In a retrospective cohort study, Fitz-Maurice et al. [2008] compared the outcome of 149 patients pretreated with statins with 480 untreated patients. They found no difference among the groups concerning mortality, functional outcome and volume of hematoma. In a small group study, Tapia-Perez et al. [2009] examined 18 patients under ruravastatin with a control group of statin non users. The mortality rate was 5.6% among users and 15.8% in the control group. In Israel, two studies have been published. Eichel et al. [2010] found that the mortality rate among 101 statin pretreated patients was 45.5%, whereas the percentage among 298 non treated patients was 56.1%, p=0.04). The other Israeli study based on the data of the Israel Stroke Survey, compared 89 patients statin pretreated patients with a 312 untreated patient group. The patients under statin treatment had a better baseline neurological status or better outcome and a lower mortality rate [Leker et al., 2009]. In a prospective ascertained cohort study, Biffi et al. [2011] compared 238 statin pretreated intracerebral hemorrhage patients with 461 non treated patients. They extended their own results into a meta analysis of previously published data – for a total of 698 vs 1,823 patients. They found a favorable outcome for pretreated patients (OR 2.8 CI 1.37-3.17) and reduced mortality (OR 0.47 CI 0.32-0.70) at 90 days. The meta analysis results confirmed this finding concerning better outcome (OR 1.1 CI 1.38-2.65) and mortality (OR 0.55 CI 0.42-0.72).

3.8.1 Summary

Most published studies indicated a better outcome and reduced mortality among pretreated statin patients having intracerebral hemorrhage. Final decision on these issues must wait for more studies and those with a greater number of participants. No data is available concerning the issue of beginning statin treatment during the acute phase of intracerebral hemorrhage.

	Probable better outcome	Possible better outcome	Inconclusive	Probable worser outcome	Possible worser outcome
AIS under statin pretreatment	+				
AIS under statin withdrawal					+
AIS under statin and IV tpa			+		
AIS under statin and IAtpa		+			
AIS under statin as acute phase therapy		+			
SAH and statins		+			
ICH and statins		+			
Probable outcome dependent upon type of statin		+			

Abbreviations: AIS-acute ischemic stroke; tpa-tissue plasminogen activator; IV- intravenous; IA-intra-arterial; SAH-subarachnoid hemorrhage; ICH-intracerebral hemorrhage

Table 1. Statin efficacy during acute stroke

4. Conclusion

There are evidences of a favorable effect of statins in the different types of stroke. The efficacy was demonstrated in ischemic and hemorrhagic stroke. Most studies show a better recovery and decrease of mortality rate among statins pretreated patients, who did not discontinued the treatment. A newly treatment with statin during the acute phase of stroke maybe indicated. The pleiotrophic effect of statins may play a key role in the positive effect of statins. It is plausible that this effect is not a class effect of the statin group, but is an individual effect of each the drugs. Much larger well designed studies must be performed to confirm these assumptions.

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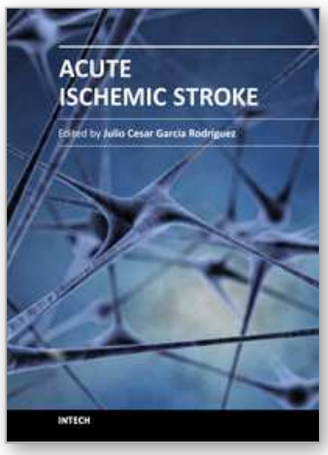

Acute Ischemic Stroke

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Despite significant technological advances in recent years, their impact on our overall health and social, well-being is not always clear to see. Perhaps, one of the best examples of this can be highlighted by the fact that mortality rates as a result of cerebrovascular diseases have hardly changed, if at all. This places cerebrovascular diseases as one of the most prominent causes of both disability and death. In Cuba, for instance, a total of 22,000 cases of cerebrovascular diseases are reported each year in a country where life expectancy should increase to 80 years in the near future. In such a situation, to have a book that includes in a clear and summarized way, a group of topics directly related to the preclinical investigations advances and the therapeutic procedures for the cerebrovascular disease in its acute phase constitutes a useful tool for the wide range of the contributors to this affection's problems solution. In this group is included students, professors, researchers, and health policy makers whose work represents one of the greatest social and human impact challenges of the XXI century basic and clinical neurosciences.

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