# LIPOPROTEIN(A) IN CEREBRAL STROKE: A REVIEW

CRISTINA RUSSO[1], MARCO VACANTE[1], GIULIA MALAGUARNERA[2], FILIPPO DRAGO[2], VELIA D'AGATA[3], LUIGI RAMPELLO[4], RITA BELLA[4], MANUELA PENNISI[4], MICHELE MALAGUARNERA[2], LIBORIO RAMPELLO[4]

[1]Department of Senescence, Urological and Neurological Sciences, University of Catania, Italy, [2]International PhD programme in Neuropharmacology, University of Catania, Italy, [3]Department "G.F. Ingrassia", [4]Department "G.F. Ingrassia", Section of Neurosciences University of Catania, Italy,

*[Lipoproteina (a) nell'ictus cerebrale. Review]*

**ABSTRACT**

Lipoprotein(a) [Lp(a)] and apolipoprotein(a) [apo(a)] levels may be risk factors for cerebrovascular diseases. Lp(a) can accumulate in the arterial walls of cerebral vessels. This happens because apo(a) can bind proteoglycans, glycosaminoglycans and fibronectin, which are important connective tissue elements. Lp(a) is implicated in the activation of endothelial uptake, oxidative modification and foam cell formation, suggesting that these processes could play an important role in atherosclerosis.

Endothelial dysfunction represents a common link in many diseases induced by elevated plasma concentrations of Lp(a) ranging from chronic inflammation to atherosclerosis and including ischemic stroke. The role of Lp(a) as a risk factor for ischemic stroke has been assessed in several studies.

The results support the hypothesis that elevated Lp(a) is a risk factor for ischemic stroke and especially for stroke caused by large artery atherosclerosis.

**Key words:** Lipoprotein(a), apolipoprotein(a), atherosclerosis, stroke, cardiovascular disease.

***Received*** *September 04, 2012;* ***Accepted*** *September 26, 2012*

## Introduction

Lipoprotein(a) was described in 1963 by Berg in the electrophoretic band of prebeta lipoprotein. It has a diameter of 25-30 nanometers and molecular weigth ranging between 280,000 and 700,000 daltons. It consists of a low-density lipoprotein (LDL)-like particle, combined with a chain of apolipoprotein(a) or apoprotein(a)[(1)]. Apoprotein(a) [Apo(a)] is linked to apolipoprotein B100 (ApoB100) by a single disulphide bridge[(2)].

The apo(a) gene is a member of the plasminogen superfamily of evolved genes. The apo(a) gene has been described in primates and the hedge-hog[(3)].

Although the relation between Lp(a) and atherosclerosis has been reported in numerous studies, little is known about whether Lp(a) would exacerbate the complicated lesion formation in vivo[(4)].

Clinical importance of Lp(a), as reported in several studies, is due to its role as a risk factor for cardiovascular diseases. It has been suggested that the atherogenic property of Lp(a) may be associated with its structural similarity to plasminogen[(5)]. Moreover, lipoprotein(a) may interfere in clot lysis by competing for the same binding sites as plasminogen.

Lp(a) is implicated in the activation of endothelial uptake, oxidative modification and cell formation, and it has been suggested that these processes play an important role in atherosclerosis. Lp(a) can accumulate in the arterial walls of coronary and cerebral vessels[(6)]. This happens because apo(a) can bind proteoglycans, glycosaminoglycans and fibronectin, which are important connective tissue elements[(7)]. Some studies demonstrate that serum Lp(a) concentrations correlate significantly with plasma fibrinogen levels[(8)]. Plasma fibrinogen level has been recognized as an independent risk factor for atherosclerosis and its thrombotic complications in adults[(9)]. Fibrinogen enhances platelet

activity, and elevated plasma fibrinogen concentrations are predictors of vascular events. Fibrinogen promotes the binding of apo(a) to the vessel walls in vivo and it is necessary for its resulting pathological effects involved in the generation of atherosclerosis[10]. Moreover, fibrinogen is an independent risk factor for ischemic atherothrombotic stroke[11].

Elevated Lp(a) levels (>25-30 mg/dl) have been linked to an increased risk of atherothrombotic diseases[12,13]. Metabolic abnormalities and pharmacological agents can influence the concentrations of Lp(a). These values can be elevated in diabetes mellitus[14], chronic renal failure[15], nephrotic syndrome[16], cancer[17-19], hypothyroidism[20] and as part of the acute phase response[21]. Lp(a) values are low in liver failure[22] and hyperthyroidism[23]. The values for Lp(a) serum levels are between 0.1 and 300 mg/dl; mean values are 18.4 mg/dl[24].

Elevated serum lipoprotein(a) is an independent predictor of coronary artery disease (CAD) and myocardial infarction[25-27], intermittent claudication[28] and cerebrovascular disease[29].

Motta et al studied the transient increased serum levels of this lipoprotein during acute myocardial infarction (AMI). The positive correlation between mean Lp(a) values on day 1 and 7, and the size of the necrotic area, suggest that Lp(a) has an atherogenic and prothrombotic role. Moreover, elevated Lp(a) values were related to increased tissue damage. The study suggests that periodical determination of Lp(a) values in subjects with coronary diseases is useful in order to predict further acute vascular events[30].

**Serum levels, structure and isoforms**

Biophysical studies of Lp(a) have revealed aspects of its structure. Lp(a) particles examined by electron microscopy appeared to be roughly circular, with no apparent differences from images of LDL (31). Cryoelectron microscope studies showed Lp(a) particles to be roughly spherical with a low-density core surrounded by a higher density shell, and some particle averages showed a toroidal structure[32]. However, it was not possible to relate these observations to other properties of Lp(a).

Apo(a) shows a specific structure, different by apoB100 with low content of aspartate, leucine, isoleucine, phenyilalanin and lysine, while proline, threonine, arginine and glycine are elevated. The high content in proline, serine and threonine in the apo(a) suggests the frequent presence of β-sheet. Moreover, serine and threonine represent glycosilation sites[33,34]

While in the apoB100 carboydrates represent 5-10% of the protein weight, in the apo(a) this value can be 40%. The percentages of carbohydrates are: 26% galactose, 9% mannose, 16% galactosamine, 12% glucosamine and 37% sialic acid.

High carbohydrates and proline levels in the apo(a) cause less structural order compared to apoB100. Apo(a) contains 8% of alpha-coil, 21% of beta-sheet and 71% of random coil, apoB100 40, 30 and 30% respectively[35].

The apo(a) product contains several sequential tertiary polypeptide coils called kringles, that are homologous with the kringle IV region of plasminogen. Some of the kringle IV units appear to contain either strong or weak lysine binding sites that contribute to the structure of the Lp(a) particle[36] and to its (sub)cellular distribution[37] and metabolism[38]. The number of sequential kringles for repeats is highly variable, comprising the primary basis for the genetic polymorphism and size heterogeneity found in humans[39].

The serine-proteinase region of apo(a) contains the same residues that constitute the potential active site in plasminogen, however, a Serine substitution at the Arginine-Valine activation cleavage site makes apo(a) insensitive to plasminogen activators[40].

Dieplinger et al discovered six different isoforms (F, B, S1, S2, S3 and S4 according to different electrophoretic mobilities) that vary in size from 300 to 800 kDa[41]. More recently, a seventh isoform category, S5, has been described. Improved techniques at higher resolution revealed >20 protein isoforms. The isoforms can be grouped into low (LMW) and high molecular weight (HMW) isoforms, according to the number of kringle IV repeats in the apo (a) molecule. In healthy subjects, LMW isoforms are associated with high levels of Lp(a) and HMW isoforms with lower levels of Lp(a). Lp(a) levels are not significantly affected by age or sex, diabetes, dietary cholesterol or HMG-CoA-reductase inhibitors[42].

**Genetics of Lp(a)**

The genetic nature of the Lp(a) lipoprotein variations in human serum was realized and reported by Berg in 1963. Single gene control was postulated and later confirmed in numerous studies, including a major study from Hawaii[43]. The gene

for the Lp(a) apolipoprotein, the LPA gene, has evolved from the gene for plasminogen, which is a much smaller protein[44]. Lp(a) concentrations exhibit only a very small amount of variation in any given individual. Classical linkage studies between segregating high Lp(a) lipoprotein levels and plasminogen polymorphism (the polymorphism in the gene that the LPA gene developed from) has confirmed an extremely close linkage.

This very strong linkage, between segregating high Lp(a) lipoprotein levels and plasminogen, by itself proves that Lp(a) level is controlled by the LPA locus on chromosome 6 or by regions very closely linked to the LPA gene. The discovery that the LPA gene has evolved from the plasminogen gene made it plausible to hypothesize that LPA genes could influence components or processes related to thrombogenesis or thrombolysis in various ways.

Berg showed the interrelationship between fibrinogen levels and Lp(a) levels; LPA genes appear to affect both the level and variability of fibrinogen; they may have "level gene" as well as "variability gene" effects on fibrinogen.

The effect of LPA genes on absolute fibrinogen level may be more pronounced at higher age than at young age. The same may be true with respect to the "variability gene" effect of LPA genes and this effect may also be stronger in women than in men[45].

## Lp(a) and stroke

Apart from the well established risk factors for stroke (such as increasing age, hypertension, diabetes, smoking, or the presence of vascular diseases), the possibility that Lp(a) may be a risk factor for ischemic stroke has been assessed in several (mainly retrospective) studies[46]. Milionis et al. suggested that determination of Lp(a) levels and Apo(a) isoform size may be important in identifying elderly individuals at risk of ischemic stroke independently of other risk factors and concurrent metabolic derangements[47].

Petersen et al in 2007 investigated whether elevated Lp(a) is more frequent in ischemic stroke related to atherothrombosis than in other etiologies of stroke. Because of the close structural homology between Lp(a) and plasminogen, they also studied the role of plasminogen in different stroke subtypes and whether a dependency on Lp(a) plasma levels exists. The results support the hypothesis that elevated Lp(a) is a risk factor for ischemic stroke and especially for stroke caused by large artery atherosclerosis. Low plasminogen activity may play a role in the pathogenesis of cerebrovascular diseases, especially for the development of cardioembolic stroke[48].

The relationship between Lp(a) and hemostatic profile was demonstrated in other studies which documented that Lp(a) seems to be more associated with coagulation markers of thrombosis[49]. Many studies documented the relationship between Lp(a) and symptomatic stroke. Nevertheless, asymptomatic, "silent", cerebral infarction has also attracted interest. A silent stroke is usually detected on incidental imaging (computed tomography scan, magnetic resonance imaging) in patients with no localised neurological signs. In most cases of silent infarction, lacunar strokes of less than 1 cm in size are detected in the basal ganglia in apparently healthy elderly individuals. These lesions are associated, in most reports, with advanced age and hypertension, and constitute a major cause of dementia.

Kario et al reported that silent multiple lacunar strokes in 178 asymptomatic, high risk, elderly Japanese patients (aged 44 to 93 years) were associated with a hypercoagulable state, endothelial damage, and significantly raised Lp(a) concentrations.

The authors further subdivided the silent lacunar group into subgroups based on the number of lacunes (few lacunes, 1–2; moderate number, 3–4; numerous lacunes, 5). Raised Lp(a) values (and particularly those > 300 mg/litre) were more common in the "numerous lacune" than the "few lacune" subgroups (50). On the other hand, there are studies that do not support Lp(a) as a risk factor for stroke. Hobbs and White proposed several factors that might contribute to the existing confusion in attributing risk to Lp(a).

*These included*:

1) small sample sizes unable to determine the relation between apo(a) phenotypes and Lp(a) concentrations,

2) different ethnic groups,

3) the influence of oestrogens in women participating in studies,

4) plasma storage before Lp(a) determination,

5) inappropriate methods of data analysis, and

6) selection bias[51].

However, on balance, there is evidence that raised circulating Lp(a) concentrations are associated with an increased risk of vascular events.

Furthermore, other risk factors (such as dyslipidaemia or raised homocysteine values) enhance the risk attributed to Lp(a). Therefore, the association between high Lp(a) values and atherosclerotic complications might be weaker in prospective studies than in cross sectional studies.

In the latter, the presence of the disease is a prerequisite and, thus, other risk factors could significantly contribute to the atherosclerotic burden[52-57].

## Conclusions

Lp(a) lipoprotein is an emerging finding in the development of atherothrombosis. Moreover, Lp(a) is an important predictor of several other diseases[58-59]. Lp(a) seems to be associated with coagulation markers of thrombosis and recent studies suggested that an increased Lp(a) level could represent a risk factor for ischemic stroke. Further studies are needed to investigate the role of Lp(a) as an established risk factor for stroke.

## References


1) Utermann G. *The mysteries of lipoprotein(a)*. Science. 1989; 246: *904-10*.
2) Marcovina SM, Gaur VP, Albers JJ. *Biological variability of cholesterol, triglyceride, low- and high-density lipoprotein cholesterol, lipoprotein(a), and apolipoproteins A-I and B*. Clin Chem. 1994; 40: *574-8*.
3) Lippi G, Guidi G. *Lipoprotein(a): from ancestral benefit to modern pathogen?* QJM. 2000; 93: *75-84*.
4) Fan J, Sun H, Unoki H, Shiomi M, Watanabe T. *Enhanced atherosclerosis in Lp(a) WHHL transgenic rabbits*. Ann N Y Acad Sci. 2001; 947: *362-5*.
5) Scanu AM. *Lipoprotein(a) as a cardiovascular risk factor*. Trends Cardiovasc Med. 1991; 1: *294-9*.
6) Rath MA, Niendorf T, Reblin M, Dietel M, Krebber HJ, Beisiegel U. *Detection and quantification of lipoprotein(a) in the arterial wall of 107 coronary bypass patients*. Arteriosclerosis 1989; 9: *579-92*.
7) Kostner GM, Bihari-Varga M. *Is the atherogenicity of Lp(a) caused by its reactivity with proteoglycans?* Eur Heart J 1990; 11: *184-9*.
8) Heinrich J, Sandkamp M, Kokott R, Schulte G. Assmann G. *Relationship of lipoprotein(a) to variables of coagulation and fibrinolysis in a healthy population*. Clin Chem 1991; 37: *1950-4*.
9) Imperatore G, Riccardi G, Iovine C, Rivellese AA, Vaccaro O. *Plasma fibrinogen: a new factor of the metabolic syndrome. A population-based study*. Diabetes Care 1998; 21: *649-54*.
10) Lou XJ, Boonmark NW, Horrigan FT, Degen JL, Lawn RM. *Fibrinogen deficiency reduces vascular accumulation of apolipoprotein(a) and development of atherosclerosis in apolipoprotein(a) transgenic mice*. Proc Natl Acad Sci U S A 1998; 95: *12591-5*.
11) Fukujima MM, Martinez TL, Pinto LE, Auriemo Cdo R, de Andrade LA. *Fibrinogen as independent risk factor for ischemic stroke*. Arq Neuropsiquiatr 1997; 55: *737-40*.
12) Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL. *Lp(a) lipoprotein as a risk factor for myocardial infarction*. JAMA. 1986; 256: *2540-4*.
13) Durrington PN, Ishola M, Hunt L, Arrol S, Bhatnagar D. *Apolipoproteins (a), AI, and B and parental history in men with early onset ischaemic heart disease*. Lancet. 1988; 1: *1070-3*.
14) Bruckert E, Davidoff P, Grimaldi A, Truffert J, Giral P, Doumith R, Thervet F, De Gennes JL. *Increased serum levels of lipoprotein(a) in diabetes mellitus and their reduction with glycemic control*. JAMA. 1990; 263: *35-6*.
15) Kronenberg F. *Lipoprotein(a) in renal disease: what we have, what we need, what we can forget*. Nephrol Dial Transplant. 1995; 10: *766-9*.
16) Stenvinkel P, Berglund L, Heimbürger O, Pettersson E, Alvestrand A. *Lipoprotein(a) in nephrotic syndrome*. Kidney Int. 1993; 44: *1116-23*.
17) Wright LC, Sullivan DR, Muller M, Dyne M, Tattersall MH, Mountford CE. *Elevated apolipoprotein(a) levels in cancer patients*. Int J Cancer. 1989; 43: *241-4*.
18) Motta M, Giugno I, Ruello P, Pistone G, Di Fazio I, Malaguarnera M. *Lipoprotein (a) behaviour in patients with hepatocellular carcinoma*. Minerva Med. 2001; 92: *301-5*.
19) Uccello M, Malaguarnera G, Pelligra EM, Biondi A, Basile F, Motta M. *Lipoprotein(a) as a potential marker of residual liver function in hepatocellular carcinoma*. Indian J Med Paediatr Oncol. 2011; 32: *71-5*.
20) Engler H, Riesen WF. *Effect of thyroid function on concentrations of lipoprotein(a)* Clin Chem. 1993; 39: *2466-9*.
21) Craig WY, Ledue TB. *Lipoprotein(a) and the acute phase response*. Clin Chim Acta. 1992; 210: *231-2*.
22) Feely J, Barry M, Keeling PW, Weir DG, Cooke T. *Lipoprotein(a) in cirrhosis*. BMJ. 1992;304:545-6.
23) Kung AW, Pang RW, Lauder I, Lam KS, Janus ED. *Changes in serum lipoprotein(a) and lipids during treatment of hyperthyroidism*. Clin Chem. 1995; 41: *226-31*.
24) Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. *Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations*. J Clin Invest. 1992; 90: *52-60*.
25) Schaefer EJ, Lamon-Fava S, Jenner JL, McNamara JR, Ordovas JM, Davis CE, Abolafia JM, Lippel K, Levy RI. *Lipoprotein(a) levels and risk of coronary heart disease in men*. The lipid Research Clinics Coronary Primary Prevention Trial. JAMA. 1994; 271: *999-1003*.
26) Rader DJ, Cain W, Ikewaki K, Talley G, Zech LA, Usher D, Brewer HB Jr. T*he inverse association of plasma lipoprotein(a) concentrations with apolipoprotein(a) isoform size is not due to differences in Lp(a) catabolism but to differences in production rate*. J Clin Invest. 1994; 93: *2758-63*.
27) Bostom AG, Gagnon DR, Cupples LA, Wilson PW, Jenner JL, Ordovas JM, Schaefer EJ, Castelli WP. *A prospective investigation of elevated lipoprotein (a) detected by electrophoresis and cardiovascular disease in women*. The Framingham Heart Study. Circulation. 1994; 90: *1688-95*.
28) Valentine RJ, Grayburn PA, Vega GL, Grundy SM. *Lp(a) lipoprotein is an independent, discriminating risk factor for premature peripheral atherosclerosis among white men*. Arch Intern Med. 1994; 154: *801-6*.
29) Murai A, Miyahara T, Fujimoto N, Matsuda M, Kameyama M. *Lp(a) lipoprotein as a risk factor for*

*coronary heart disease and cerebral infarction*. Atherosclerosis. 1986; 59: *199-204*.

30) Motta M, Giugno I, Bosco S, Pistone G, Ruello P, Maugeri D, Malaguarnera M. *Serum lipoprotein(a) changes in acute myocardial infarction*. Panminerva Med. 2001; 43: *77-80*.

31) Edelstein C, Italia JA, Klezovitch O, Scanu AM. *Functional and metabolic differences between elastase-generated fragments of human lipoprotein[a] and apolipoprotein[a]*. J Lipid Res. 1996; 37: *1786-801*.

32) Sines J, Rothnagel R, van Heel M, Gaubatz JW, Morrisett JD, Chiu W. *Electron cryomicroscopy and digital image processing of lipoprotein(a)*. Chem Phys Lipids. 1994; 67-68: *81-9*.

33) Koschinsky ML, Marcovina SM, May LF, Gabel BR. *Analysis of the mechanism of lipoprotein(a) assembly*. Clin Genet. 1997; 52: *338-46*.

34) Mims MP, Soma MR, Morrisett JD. *Effect of particle size and temperature on the conformation and physiological behavior of apolipoprotein E bound to model lipoprotein particles*. Biochemistry. 1990; 29: *6639-47*.

35) Lee BR, Miller JM, Yang CY, Ramdas L, Yang ML, Morrisett JD, Mims MP. *Amino acid sequence of rabbit apolipoprotein E*. J Lipid Res. 1991; 32: *165-71*.

36) Ernst A, Helmhold M, Brunner C, Pethö-Schramm A, Armstrong VW, Müller HJ. *Identification of two functionally distinct lysine-binding sites in kringle 37 and in kringles 32-36 of human apolipoprotein(a)*. J Biol Chem. 1995; 270: *6227-34*.

37) Boonmark NW, Lawn RM. *The lysine-binding function of Lp(a)*. Clin Genet. 1997; 52: *355-60*.

38) Argraves KM, Kozarsky KF, Fallon JT, Harpel PC, Strickland DK. T*he atherogenic lipoprotein Lp(a) is internalized and degraded in a process mediated by the VLDL receptor.* J Clin Invest. 1997;100:2170-81.

39) Kraft HG, Lingenhel A, Köchl S, Hoppichler F, Kronenberg F, Abe A, Mühlberger V, Schönitzer D, Utermann G. *Apolipoprotein(a) kringle IV repeat number predicts risk for coronary heart disease*. Arterioscler Thromb Vasc Biol. 1996; 16: *713-9*.

40) McLean JW, Tomlinson JE, Kuang WJ, Eaton DL, Chen EY, Fless GM, Scanu AM, Lawn RM. *cDNA sequence of human apolipoprotein(a) is homologous to plasminogen*. Nature. 1987; 330: *132-7*.

41) Dieplinger H, Lackner C, Kronenberg F, Sandholzer C, Lhotta K, Hoppichler F, Graf H, König P. *Elevated plasma concentrations of lipoprotein(a) in patients with end-stage renal disease are not related to the size polymorphism of apolipoprotein(a)*. J Clin Invest. 1993; 91: *397-401*.

42) Parsons DS, Reaveley DA, Pavitt DV, Misra M, Brown EA. *Lipoprotein (a) levels in those with high molecular weight apo (a) isoforms may remain low in a significant proportion of patients with end-stage renal disease*. Nephrol Dial Transplant. 2003; 18: *1848-53*.

43) Berg K. *Lp(a) lipoprotein: an overview*. Chem Phys Lipids. 1994; 67-68: *9-16*.

44) Lawn RM, Wade DP, Hammer RE, Chiesa G, Verstuyft JG, Rubin EM. *Atherogenesis in transgenic mice expressing human apolipoprotein(a) Nature*. 1992; 360: *670-2*.

45) Berg K, Dahlén G, Christophersen B, Cook T, Kjekshus J, Pedersen T. *Lp(a) lipoprotein level predicts survival and major coronary events in the Scandinavian Simvastatin Survival Study*. Clin Genet. 1997; 52: *254-61*.

46) Milionis HJ, Winder AF, Mikhailidis DP. *Lipoprotein (a) and stroke*. J Clin Pathol 2000; 53: *487-496*.

47) Milionis HJ, Filippatos TD, Loukas T, Bairaktari ET, Tselepis AD, Elisaf MS. *Serum lipoprotein(a) levels and apolipoprotein(a) isoform size and risk for first-ever acute ischaemic nonembolic stroke in elderly individuals*. Atherosclerosis 2006; 187: *170-6*.

48) Petersen NH, Schmied AB, Zeller JA, Plendl H, Deuschl G, Zunker P. *Lp(a) lipoprotein and plasminogen activity in patients with different etiology of ischemic stroke*. Cerebrovasc Dis 2007; 23: 188-93.

49) Kronenberg F, Steinmetz A, Kostner GM, Dieplinger H. *Lipoprotein(a) in health and disease*. Crit Rev Clin Lab Sci 1996; 33: *495-543*.

50) Kario K, Matsuo T, Kobayashi H, Asada R, Matsuo M. *"Silent" cerebral infarction is associated with hypercoagulability, endothelial cell damage, and high Lp(a) levels in elderly Japanese*. Arterioscler Thromb Vasc Biol 1996; 16: *734-41*.

51) Hobbs HH, White AL. Lipoprotein(a): intrigues and insights. Curr Opin Lipidol 1999; 10: *225-36*.

52) Coleman MP, Key TJ, Wang DY, Hermon C,. Fentiman IS, Allen DS, Jarvis M, Pike MC, Sanders TA. *A prospective study of obesity, lipids, apolipoproteins and ischaemic heart disease in women*. Atherosclerosis 1992; 92: *177-185*.

53) Jauhiainen M, Koskinen P, Ehnholm C, Frick MH, Mänttäri M, Manninen V, Huttunen JK. Lipoprotein (a) and coronary heart disease risk: a nested case-control study of the Helsinki Heart Study participants. Atherosclerosis 1991;89:59-67.

54) Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. *Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality*. JAMA 2009; 302: *412-23*.

55) Salomone S, Drago F, Effects of PPARγ Ligands on Vascular Tone., Curr Mol Pharmacol. 2012; 5(2):282-91.

56) Salomone S, *Pleiotropic effects of glitazones: a double edge sword?*, Front Pharmacol. 2011; 2: *14*.

57) Bucolo C, Leggio GM, Drago F, Salomone S, *Eriodictyol prevents early retinal and plasma abnormalities in streptozotocin-induced diabetic rats*, Biochem Pharmacol. 2012 84(1): *88-92*.

58) Galvano F, Malaguarnera M, Vacante M, Motta M, Russo C, Malaguarnera G, D'Orazio N, Malaguarnera L. *The physiopathology of lipoprotein (a)*. Front Biosci (Schol Ed). 2010; 2: *866-75*.

59) Zelante G, Catalano A, Ricceri R, Rampello L, Rampello L. *La demenza vascolare sottocorticale: luci ed ombre,* Acta Medica Mediterranea, 2012, 28: *45-52*.

*Acknowledgements*

*Dr. Michele Malaguarnera and Giulia Malaguarnera were supported by the International Ph.D. Programme in Neuropharmacology, University of Catania, Catania, Italy.*

*Request reprints from:*
Prof. LIBORIO RAMPELLO
Direttore U.O.C. di Neurofisiopatologia
Padiglione 2 (Neurologia)
Policlinico dell'Università di Catania
V. Santa Sofia 78
95100 Catania
*(Italy)*