Leaders

Lipoprotein (a) and stroke

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Abstract
Strokes are one of the most common causes of mortality and long term severe disability. There is evidence that lipoprotein (a) (Lp(a)) is a predictor of many forms of vascular disease, including premature coronary artery disease. Several studies have also evaluated the association between Lp(a) and ischaemic (thrombotic) stroke. Several cross sectional (and a few prospective) studies provide contradictory findings regarding Lp(a) as a predictor of ischaemic stroke. Several factors might contribute to the existing confusion—for example, small sample sizes, different ethnic groups, the influence of oestrogens in women participating in the studies, plasma storage before Lp(a) determination, statistical errors, and selection bias. This review focuses on the Lp(a) related mechanisms that might contribute to the pathogenesis of ischaemic stroke. The association between Lp(a) and other cardiovascular risk factors is discussed. Therapeutic interventions that can lower the circulating concentrations of Lp(a) and thus possibly reduce the risk of stroke are also considered.
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Strokes (cerebrovascular accidents) are considered to be one of the most common causes of mortality and long term severe disability.[1] It is well documented that hyperlipidaemia is a powerful risk factor for ischaemic heart disease (IHD).[2–4] However, it was not until recently that the important role of lipids in the prevention of strokes was identified.[5] There is a positive correlation between serum total cholesterol (TC) concentrations and ischaemic (thrombotic) stroke, and very low TC concentrations have been associated with an increased risk of haemorrhagic stroke. Raised low density lipoprotein cholesterol (LDL) or triglyceride (TG) concentrations, reduced high density lipoprotein cholesterol (HDL) concentrations, and a high TC to HDL ratio are associated with an increased risk of non-haemorrhagic stroke.[5] There is evidence that lipoprotein (a) (Lp(a)) is a predictor of many forms of vascular disease, including premature coronary artery disease.[6] Studies in subjects with average

lipid profiles indicate that raised serum Lp(a) concentrations are associated with myocardial infarction, coronary stenosis, re-occlusion of aortocoronary bypass vein grafts, peripheral atherosclerosis, and cerebral ischaemia.[6–8]

In this review, we focus on the possible role of Lp(a) in the pathogenesis of ischaemic (thrombotic) stroke. We scanned the National Library of Medicine (USA) search service in MEDLINE and Pre-MEDLINE (with links to participating online journals) and other related databases. Our research covered all languages and the years between 1962 and October 1999. The keywords were stroke, cerebrovascular accident, and Lp(a).

Lp(a): a link between atherogenesis and fibrinolysis
THE STRUCTURE OF Lp(a)
Lp(a) is an LDL like molecule consisting of an apoprotein (apo) B-100 particle attached by a disulphide bridge to apo(a).[6] Apo(a) is a member of a family of "kringle" containing proteins, such as plasminogen, tissue platelet activator (tPA), prothrombin, factor XII, and macrophage stimulating factor (MSF).[9 10] Lp(a) shares a high degree of sequence identity with plasminogen.[9 11]

The apo(a) gene is highly polymorphic; more than 34 different sized alleles have been identified.[12] Corresponding isoforms with molecular weights ranging from 187 to 648 kDa were identified in human serum.[13 14] The size polymorphism of apo(a) is mainly the result of the genetically determined number of kringle IV type 2 repeats.[12]

MODULATION OF PLASMA Lp(a) CONCENTRATIONS
Plasma Lp(a) concentrations are variable and their distribution in the general population is highly skewed (approximately 90% of the population has serum values less than 300 mg/litre; occasional patients have values above 20000 mg/litre.[15] Lp(a) exhibits a high degree of heritability through kringle isoform transmission.[16] Nevertheless, certain metabolic abnormalities, as well as pharmacological agents, can influence the circulating concentrations of Lp(a). These values can be increased as part of the acute phase response,[17] and in diabetes mellitus,[18] chronic renal failure,[19–21] nephrotic syndrome,[22 23] cancer,[24] menopause, and hypothyroidism.[25] The potential rise in circulating Lp(a) concentrations as part of the

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acute phase response is of special interest because the atherosclerotic process is thought to have an inflammatory component.[26] Therefore, serum Lp(a) concentrations could perhaps be influenced by the presence of extensive vascular disease. Lp(a) values are decreased in liver failure[27] and hyperthyroidism.[28] Furthermore, nicotinic acid,[29] tamoxifen,[30] oestrogens,[31] progesterone, and anabolic steroids[32] might decrease Lp(a) concentrations. Fibrates have been shown, in some studies, to reduce Lp(a) concentrations,[33 34] whereas statins might increase Lp(a) concentrations.[35–37]

APO(a) GENE POLYMORPHISM AND PHENOTYPES

Plasma Lp(a) concentrations are inversely correlated with the size of the apo(a) isoform.[38] For example, significantly raised Lp(a) concentrations in patients with rheumatoid arthritis were caused mainly by an increase in the S3 (low molecular weight) isoform.[39] However, recent evidence suggests that the contribution of the apo(a) isoform size to the control of plasma Lp(a) concentrations is considerably lower than previously thought. This is because the variability in plasma Lp(a) concentration is not uniform across the apo(a) size spectrum.[16 40] It is still unclear whether further apo(a) gene polymorphism (not affecting the size of the Lp(a) molecule) influences the circulating concentrations of Lp(a).[41] Small (low molecular weight) isoforms are usually associated with higher total Lp(a) values (probably because assembly is less complex and thus faster) and a higher risk of atherogenesis compared with the large (high molecular weight) isoforms.[42] It is also worth considering that the risk attributed to Lp(a) might not be continuous. Thus, very high concentrations might be substantially more dangerous than values closer to the epidemiological cut off value of 300 mg/litre.[26] Whether the risk of stroke associated with a moderate increase of Lp(a) is conditioned by the coexisting LDL concentrations remains to be established.

THE PATHOPHYSIOLOGICAL LINK BETWEEN Lp(a) AND ATHEROTHROMBOSIS

The accumulation of Lp(a) molecules has been demonstrated in the arterial walls of human coronary and cerebral vessels.[43] This process might be attributed to the tendency of apo(a) to bind to connective tissue elements, such as proteoglycans, glycosaminoglycans, and, especially, fibronectin.[44] This binding process is promoted by lipoprotein lipase or sphingomyelinase.[45]

Lp(a) particles are susceptible to oxidative modification and scavenger receptor uptake, leading to intracellular cholesterol accumulation and foam cell formation,[46 47] which contributes further to atherogenesis. The raised sialic acid content of Lp(a) is thought to contribute to the oxidative resistance of the native particle.[47] The prothrombotic action of Lp(a) is, however, far more well established. Because of the structural homology with plasminogen, Lp(a) might have important antithrombolytic properties, which could contribute to the pathogenesis of atherothrombotic disease. For example, Lp(a) binding to immobilised fibrinogen and fibrin results in the inhibition of plasminogen binding to these substrates.[48] In addition, Lp(a) competes with plasminogen for its receptors on endothelial cells, leading to diminished plasmin formation, thereby delaying clot lysis and favouring thrombosis.[48] The high affinity of Lp(a) for fibrin provides a mechanistic basis for their frequent colocalisation in atherosclerotic plaques.[49 50]

In vitro studies indicate that Lp(a) enhances the synthesis of plasminogen activator inhibitor 1 (PAI-1) by endothelial cells. PAI-1 is the main inhibitor of the fibrinolytic system.[51] Another potentially important action of Lp(a) is that by displacing plasminogen from the surfaces of macrophages in atherosclerotic plaques, it reduces the activation of latent transforming growth factor β (TGF-β). In the absence of activated TGF-β, cytokines might induce smooth muscle cell proliferation and the transformation of these cells to a more atherogenic cellular phenotype.[52]

The relative importance of oxidation or thrombogenic mechanisms is difficult to establish at this stage.

THE RELATION BETWEEN Lp(a) AND ATHEROSCLEROSIS

The question of whether Lp(a) plays a primary or synergistic role in atherosclerosis has been investigated recently.[53] Almost all cross sectional and retrospective studies involving white men have shown an increased risk of coronary, peripheral, and cerebrovascular atherosclerotic disease associated with plasma Lp(a) concentrations greater than the 80th centile (> 250–300 mg/litre). Prospective studies have provided controversial data. However, cross sectional and retrospective studies could be misleading because of selection bias or the effect that the disease itself can have on the studied parameter.[53] Furthermore, storage of the samples and the use of suboptimal Lp(a) assays might interfere in the interpretation of the results.[53] Nevertheless, most of the more recent prospective studies revealed a modest significant association between IHD and raised plasma Lp(a) concentrations.[54–56]

Another question that has been raised is whether atherosclerosis itself can cause high plasma Lp(a) concentrations. In this context, it is relevant that patients with IHD as well as children with a positive family history of IHD commonly exhibit small apo(a) phenotypes.[42 57] This association of small apo(a) isoforms with higher Lp(a) concentrations suggests that raised Lp(a) concentrations antedate the atherosclerotic process.[53]

Lp(a) and other thrombotic risk factors

Lp(a) AND FIBRINOGEN

Serum Lp(a) concentrations correlate significantly with plasma fibrinogen values in some, but not all, studies.[58 59] This association is of interest because platelet activity is enhanced by fibrinogen,[60 61] and raised plasma fibrinogen concentrations are predictors of vascular events, both in healthy populations and in

patients with IHD.[62] In the Goettingen risk incidence and prevalence study (GRIPS), Lp(a) and fibrinogen concentrations proved to be of value in estimating the risk of myocardial infarction.[63] Data from GRIPS and the European concerted action on thrombosis and disabilities (ECAT) studies support the hypothesis that fibrinogen is a particularly important risk factor for acute coronary events in patients with asymptomatic or overt IHD.[64 65]

There is strong evidence that fibrinogen is an independent risk factor for ischaemic atherothrombotic stroke.[66] Fibrinogen values remain significantly raised after stroke, and are associated with an increased risk of recurrent vascular events.[67] In patients with stroke, fibrinogen is associated with a decrease in white blood cell elasticity and red blood cell deformability, and an increase in plasma erythrocyte viscosity.[68] Fibrinogen also promotes platelet aggregation and consumption in the ischaemic area in patients with stroke.[69]

In this context, fibric acid derivatives can reduce the circulating concentrations of Lp(a) and fibrinogen.[64 70 71] Therefore, the platelet inhibitory activity of fibric acid derivatives could be mediated via their action on lipid fractions (mainly TG and HDL), Lp(a), and/or fibrinogen.[72 73] The preliminary results of two recently presented fibrate trials are discussed below.

Lp(a) AND HOMOCYSTEINE
Even a moderate rise in the circulating concentration of homocysteine is associated with an increased risk of atherosclerosis and arterial or venous thrombosis.[74 75] There is epidemiological evidence showing that the risk of vascular events is increased in those with a concomitant rise of both Lp(a) and homocysteine.[76] This association is of interest because both Lp(a) and homocysteine can have unwanted effects on platelets as well as on coagulation and fibrinolysis. Experimental data showed that hyperhomocysteinaemia is associated with increased platelet aggregability and thromboxane A_2 (TXA$_2$) release.[77] TXA$_2$ is a vasoconstrictor and a promoter of platelet aggregation. Homocysteine has a low mitogenic effect on vascular smooth muscle cells, but it enhances the mitogenic properties of platelet derived growth factor BB (PDGF-BB).[78] Of the PDGF stored in human platelets, 30% is in the PDGF-BB form; the remainder is in the PDGF-AB form.[79]

There is epidemiological evidence that homocysteine is a strong predictor of ischaemic stroke.[80] Moderate increases in homocysteine values (even within the population reference range) are associated with vascular pathology through a variety of mechanisms, including atherosclerosis and thrombosis.[80] Homocysteine concentrations are influenced by renal function and vitamin B$_{12}$ status in patients with stroke.[81]

Homocysteine, Lp(a), and fibrinogen probably interact to promote atherosclerosis.[82] Therefore, it is likely that their clustering increases the risk of vascular events. This possibility deserves further investigation. There is already evidence, from epidemiological studies, indicating that the dyslipidaemia + raised Lp(a) and dyslipidaemia + raised fibrinogen combinations increase the risk of vascular events.[63 83 84]

Lp(a) AND OTHER CARDIOVASCULAR RISK FACTORS
Plasma concentrations of Lp(a), TC, TG, and very low density lipoprotein (VLDL) cholesterol are higher in patients with hypertension.[85 86] It has been shown recently that raised Lp(a) concentrations and the presence of low molecular weight apo(a) isoforms are strong and independent risk factors for IHD in patients with hypertension.[87]

The data on Lp(a) concentrations in diabetes are largely based on small studies and are conflicting. Larger studies and those including apo(a) phenotype analysis suggest that Lp(a) concentrations are not different from those in patients without diabetes, or are at most only moderately raised in patients with insulin dependent diabetes.[85] However, there is evidence that Lp(a) concentrations are raised in patients with diabetes associated renal function impairment. Furthermore, atherosclerotic complications in patients with diabetes are associated with higher Lp(a) concentrations.[85]

Cigarette smoking is associated with increased values of LDL, TG, and VLDL and decreased concentrations of HDL. However, no direct effect on Lp(a) values has been reported in smokers.[88]

There is some controversy about the effect of obesity on Lp(a). In one study, Lp(a) concentrations were not influenced by obesity, visceral fat content, or weight loss after a very low energy diet.[89] However, there is also some evidence that obese individuals have higher Lp(a) values and that weight loss (by diet or surgical intervention) is associated with a significant reduction in these values.[90 91] The mechanism(s) responsible for these changes remain(s) to be defined.

Lipid variables and the risk of stroke
TC AND STROKE
Early studies did not suggest that raised serum TC values consistently predict stroke related mortality.[92 93] Indeed, in some studies, TC values were inversely related to death as a result of stroke.[94] In a meta-analysis of 13 000 strokes in a total of 450 000 people, no significant association between serum TC concentrations and stroke was found.[95] In the Framingham heart study,[96] TC concentrations were positively related to stroke mortality in women aged less than 55 years, whereas a U-shaped association was seen in women older than 55, and an inverse relation between TC and short term (within five years) mortality in women older than 70 years of age. In Israel, Korn-Lubetzki *et al* found that patients with stroke had low serum TC and LDL cholesterol values.[97] These early results might have been inconclusive in demonstrating an association between lipid concentrations and stroke because ischaemic and haemorrhagic strokes were not differentiated.

Epidemiological surveys showed an inverse association between TC values and the risk of intracerebral haemorrhage, independently of age and sex.[98–107] Specifically, 54 385 Swedish men and women participated in a health survey with serum cholesterol and diastolic blood pressure determinations.[101] The follow up period was 20.5 years (1964 to 1985). The relative risk for subarachnoid haemorrhage in men, but not in women, increased with decreasing TC values.[101] In women, the relative risk for intracerebral haemorrhage was inversely related to TC values. For cerebral haemorrhage in men, the risk function was U-shaped.[101] Adjustment for diastolic blood pressure did not significantly change the relation between the risk for any of the different stroke types and the cholesterol values.[101] Furthermore, a large cohort (61 756 subjects aged 40 to 89 years) study was performed in the San Francisco-Oakland metropolitan area from 1977 to 1985.[100] The average follow up period was 10.7 years. In this study, an association between low TC values and increased risk for intracerebral haemorrhage was confined to elderly men (aged 65 years or older).[100] In more recent studies, such as the multiple risk factor interventional trial (MRFIT), a positive relation between serum TC values and non-haemorrhagic strokes was shown, whereas serum TC values were inversely related to intracranial haemorrhage.[102 103] In a case control study, conducted from 1990 to 1992 in Italy, Di Mascio and colleagues[107] showed a strong linear relation between TC concentrations and the risk for myocardial infarction ($p < 0.0001$). However, a significant linear trend in risk was also found between TC values and ischaemic stroke ($p < 0.01$).[107]

Although it has been shown that serum TC is an independent factor for stroke[104] and transient ischaemic attacks (TIA),[105] the relation between TC and ischaemic stroke does not seem to be as strong as it is with IHD,[106 107] perhaps because different pressure gradients and vessels are involved. When considering large studies (for example, the Honolulu heart study in migrants from Japan and the MRFIT screening study), an increase in non-haemorrhagic stroke was seen at the highest, but not intermediate, concentrations of TC.[106]

TG CONCENTRATIONS AND STROKE
Interestingly, it has been shown that postprandial hypertriglyceridaemia is associated with carotid artery atherosclerosis.[108] However, there is controversy regarding the association between serum TG values and the risk of stroke.[5] Nevertheless, in the Copenhagen City heart study,[109] a log linear association between serum TG concentrations and non-haemorrhagic stroke was found (relative risk, 1.12/1 mmol/litre increase in serum TG; 95% confidence interval, 1.07 to 1.16); this association was independent of age and sex.

HDL CHOLESTEROL AND STROKE
In general, most case control studies reported an inverse association between HDL cholesterol and stroke risk.[5] Although no association was found in the Framingham study,[110] in the Copenhagen City heart study[109] a negative relation was evident (relative risk, 0.53; 95% confidence interval, 0.34 to 0.83).

APOLIPOPROTEIN E PHENOTYPES AND STROKE
Apolipoprotein E (apoE) phenotypes have been associated with strokes.[111] Pedro-Bodet *et al*, in a case control study,[111] showed that the frequency of the apoE4 gene is high in patients with ischaemic stroke. In addition, it has been shown that the apoE3/E3 phenotype has a "protective" association with stroke, because it was present more frequently in stroke free controls than in patients with ischaemic stroke.[111] In contrast, the apoE2 genotype is a risk factor possibly expressed through any concurrent obesity, diabetes, or hypertension.[112]

GEOGRAPHICAL VARIATION IN THE INCIDENCE OF STROKE
It has been reported that in Japan and China, the age standardised annual death rate from stroke is greater than that of IHD, whereas in Northern Europe and the USA the IHD associated mortality is three to four times greater than the stroke related deaths.[5 113] The increased stroke mortality in Japan might be related to a higher proportion of haemorrhagic strokes.[113] In contrast, in Mediterranean countries, deaths as a result of both IHD and stroke display an approximate 1 : 1 ratio.[113] Serum TC values, smoking, alcohol intake, and traditional diets account for these differences.[5 114] Unfortunately, we are not aware of extensive epidemiological studies that compared Lp(a) values in these nations. However, there is some evidence that median serum Lp(a) values are very similar in American white and Chinese individuals (90 and 80 mg/litre, respectively).[16] There also appeared to be a shift towards apo(a) alleles of larger sizes in the Chinese.[16]

Lp(a) and stroke
Apart from the well established risk factors for strokes (such as increasing age, hypertension, diabetes, smoking, or the presence of vascular disease),[1 5] the possibility that Lp(a) is a risk factor for ischaemic stroke has been assessed in several (mainly retrospective) studies (table 1).

STUDIES SUPPORTING Lp(a) AS A RISK FACTOR FOR STROKE
In a case control study, serum Lp(a) values were significantly ($p < 0.001$) higher in patients with ischaemic stroke compared with healthy individuals (median, 95 *v* 50 mg/litre).[115] This difference was also evident in a subgroup of subjects aged 30 to 69 years ($p < 0.001$).[115]

Lindgren *et al* determined lipid variables in 131 patients six months after their stroke.[116] These patients had higher TG and Lp(a) values and lower TC, LDL, and HDL concentrations compared with controls.

Vavernova *et al* investigated Lp(a) values in 45 patients with stroke (younger than 55 years of age) and their first degree relatives.[117] They

reported that Lp(a) values were genetically conditioned in patients with ischaemic strokes.

With regard to the genetic control of plasma Lp(a) concentrations, Jurgens et al determined Lp(a) values and apo(a) phenotypes in a consecutive series of 265 patients with ischaemic stroke in comparison with 288 controls.[118] They suggested that raised Lp(a) concentrations comprise a primary risk factor associated with the presence of this disease. In addition, they demonstrated that low molecular weight ($\leqslant$ 580 kDa) apo(a) isoforms were more frequent in the patients with stroke (42.65% *v* 16.73%; p < 0.001). Peynet et al evaluated the Lp(a) concentration and apo(a) isoform size in 90 young patients (mean age: 37.4 years) with acute cerebral ischaemia compared with those of age and sex matched controls.[119] They showed that serum Lp(a) concentrations were significantly increased in the patients with stroke (p = 0.009). However, there was no difference in the apo(a) isoform distribution between patients and controls.[119]

Van Kooten and colleagues[120] assessed Lp(a) concentrations in 151 consecutive patients admitted because of acute cerebral ischaemia. They found that in about one third of patients Lp(a) values were significantly raised, but this increase was not associated with the cardiovascular risk profile, stroke characteristics, or the prognosis.

In a recent cross sectional study, Lp(a), PAI-1, and tPA were determined in patients with and without a history of stroke.[121] After studying a total of 210 patients (half with a history of ischaemic stroke), a relation between Lp(a) and cerebral ischaemia was found. This was limited to individuals below 70 years with raised (> 500 mg/litre) plasma Lp(a) values.[121]

Nagayama et al, in a case control study, investigated Lp(a) values in patients after a mean period of 27 months since their stroke.[122] Lp(a) was a crucial and independent risk factor for ischaemic stroke, but not for lacunar stroke (< 1 cm² in size), especially in young adults.[122]

Peng et al investigated the relation between serum lipids, apoE genotypes, and the risk of ischaemic stroke.[123] They studied 90 patients who experienced an acute ischaemic stroke versus 90 healthy individuals. Serum Lp(a) concentrations and the apoE4 genotype were the prominent lipid predictors for ischaemic

stroke in addition to the more established risk factors such as hypertension, family history of stroke, and cigarette smoking.[123]

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.[124] These findings are a predisposing factor for subsequent overt stroke.[124] In most cases of silent infarction, lacunar strokes of less than 1 cm² in size are detected in the basal ganglia in apparently healthy elderly people.[125] These lesions are associated, in most reports, with advanced age and hypertension, and constitute a major cause of dementia.[124 125] Kario and colleagues[126] 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, $\geqslant$ 5). Raised Lp(a) values (and particularly those > 300 mg/litre) were more common in the "numerous lacune" than the "few lacune" subgroups.[126]

In the atherosclerosis risk in communities (ARIC) study, the association of Lp(a) with stroke was investigated in 15 160 participants (4160 blacks and 11 000 whites).[127] In this study, Lp(a) was an independent risk factor for strokes and TIA, in both blacks and whites. The relative risk of Lp(a) associated stroke morbidity was not influenced by race.[127]

This evidence might indicate that the mean Lp(a) concentration is higher in patients with atherothrombotic brain infarction than in those with brain haemorrhage or lacunar infarction.[128]

Patients with IHD are at an increased risk of having a stroke.[5] Thus, a selection bias might influence the relation between Lp(a) and risk of stroke because of an association between IHD and Lp(a) values.

STUDIES NOT SUPPORTING Lp(a) AS A RISK FACTOR FOR STROKE

The link between Lp(a) and stroke has been disputed by some investigators. Hachinski et al,[129] in a case control study, determined lipid variables, including Lp(a), in 90 patients with stroke or TIA of atherothrombotic origin. Increased LDL and TG concentrations correlated with atherothrombotic stroke risk, whereas there was no significant difference in the Lp(a) concentrations or the distribution of apoE phenotypes among patients and controls.[129]

The possibility of predicting ischaemic stroke by the determination of plasma Lp(a) concentrations and antibodies to *Chlamydia pneumoniae* was investigated by Glader et al.[130] They studied 101 subjects who had suffered an ischaemic cerebral infarction and 201 controls. No association between baseline plasma Lp(a) values, the presence of anti-*C pneumoniae* antibodies, and future ischaemic cerebral infarc-

Table 1 Studies evaluating the role of lipoprotein (a) as a risk factor for ischaemic stroke

For	Against
Jurgens and Koltringer (1987)[115]	Hachinski et al (1996)[129]
Lindgren et al (1992)[116]	Glader et al (1999)[130]
Vavernova et al (1993)[117]	Alfthan et al★ (1994)[131]
Jurgens et al (1995)[118]	Physicians' health study★ (1995)[132]
Peynet et al (1999)[119]	
Van Kooten et al (1996)[120]	
Margaglione et al (1996)[121]	
Nagayama et al (1994)[122]	
Peng et al (1999)[123]	
Kario et al (1996)[126]	
ARIC study★ (1994)[127]	
Ichinose et al (1998)[128]	

Studies are cited in the order that they appear in the text.
Parentheses show the year of publication.
★Prospective study.

tions was found. There was no evidence of an interactive effect between high Lp(a) values and anti-*C pneumoniae* antibody titres.[130]

In a prospective study in Finland, no association was found between Lp(a) or homocysteine values and atherosclerotic disease (myocardial infarction or stroke) in logistic regression analyses among 7424 men and women aged 40–60 years without atherosclerotic disease at baseline.[131] There were 134 events (myocardial infarction or stroke) in men and 131 in women.[131] However, the lack of association between homocysteine values and the myocardial infarction/stroke end point might have been the result of the exceptionally low gene frequency predisposing to homocysteinaemia in Finland.[131]

A cohort of 14 916 predominantly white, healthy, middle aged male physicians (physicians' health study) was followed prospectively for a period of 7.5 years.[132] These subjects had no previous history of stroke, TIA, or myocardial infarction. During follow up, 198 physicians developed a stroke (155 thromboembolic, 35 haemorrhagic, and eight indeterminate).[132] Their samples were analysed for Lp(a) together with paired controls, matched for age and smoking habit. Among the subjects participating in the study, no association between baseline plasma concentration of Lp(a) and future risk of total (all types of stroke) or thromboembolic stroke was found.[132]

Atherosclerotic lesions in intracranial vessels

LIPIDS AND ATHEROSCLEROSIS OF THE CEREBRAL ARTERIES

Evidence from experimental data suggested that the intracranial arteries are relatively resistant to cholesterol related endothelial damage.[133–135] Thus, studies in primates failed to show an association between the hyperlipidaemic state and the development of atherosclerosis in intracranial arteries.[133] Studies with cynomolgus and rhesus monkeys fed a hyperlipidaemic diet for eight to 12 months showed that the atherosclerotic lesions in their carotid arteries were more extensive than those in the basilar, vertebral, and middle cerebral arteries.[134] However, the coexistence of hypertension and hypercholesterolaemia resulted in accelerated atherosclerosis of intracranial arteries in rat models.[135]

Studies based on human necropsies have shown that atherosclerotic changes in cerebral arteries make their appearance 20 years later than in the coronary arteries.[136] Differences in the prevalence and extent of atherosclerotic lesions in the aorta and coronary or cerebral arteries were observed between different age and race groups. Black individuals and older people tend to have more extensive cerebral atherosclerosis.[136] Interestingly, Postiglione and colleagues[137] reported that no atherosclerotic lesions were found in the cerebral arteries of young patients with homozygous familial hypercholesterolaemia, despite a severe involvement of all the other vascular beds.

It has been proposed that the paucity of pinocytic vesicles in the endothelium of cerebral arteries, their rich innervation, and the lower distending pressures make these vessels more resistant to hyperlipidaemia compared with coronary or peripheral arteries.[136]

LIPIDS AND ATHEROSCLEROTIC CHANGES IN CAROTID ARTERIES

In a recent study of 79 patients, Landray *et al* showed that age and smoking history predicted carotid atherosclerosis, whereas the LDL score was of a borderline significance.[138] Furthermore, there was evidence that small, dense LDL subfractions were associated with carotid atherosclerosis and might be a modifiable risk factor for strokes and IHD.[138]

In an experimental model of occlusive arterial thrombus formation in cynomolgus monkeys, high Lp(a) values were associated with permanent cessation of flow and occlusive arterial thrombosis.[139] Analysis of the damaged arterial segments indicated incorporation of Lp(a) into the adventitia, media, and intima.[139]

Jurgens and Koltringer[140] studied 808 randomly selected patients (with positive stroke history as well as asymptomatic subjects). Plasma Lp(a) values correlated with carotid atherosclerosis in subjects younger than 60 years of age.[140]

It has been suggested that apo(a) can cause endothelial dysfunction by enhancing lipid deposition in vessel walls, inhibiting fibrinolysis, and modulating smooth muscle cell proliferation.[26] Moreover, Watts and colleagues[141] measured lipid variables (including Lp(a)) in 49 white patients with TIA undergoing carotid angiography. Raised Lp(a) concentrations were a significant determinant of the extent of carotid atherosclerosis. Therefore, the measurement of serum Lp(a) concentrations might help identify patients with an increased risk of stroke.[141]

Lipid associations with stroke might result from emboli originating in the aortic arch.[142 143] However, it is still not clear whether lipid lowering treatment greatly reduces the risk of this complication of atherosclerotic disease. Endothelial dependent vasomotor tone is also related to lipoprotein values but the implications for cerebral events are not yet determined.[144]

Can serum Lp(a) values be reduced?

DIETARY MODIFICATION

Diet is not thought to influence Lp(a) values to any great extent. However, saturated and n-3 polyunsaturated fatty acids may slightly reduce Lp(a) values. Thus, a diet rich in palm oil has been reported to reduce Lp(a) concentrations by approximately 10%.[145] In one study, a short term diet with n-3 polyunsaturated fatty acids had no significant effect on Lp(a) concentrations, but long term administration reduced these values by as much as 20%.[146]

NICOTINIC ACID

Nicotinic acid has a favourable, although inconsistent, effect on Lp(a) concentrations.[5 29] However, this drug is difficult to tolerate at the high doses required.

STATINS

Interestingly, a recently published overview of all randomised trials of statin treatment demonstrated that large reductions in TC values are associated with significant benefit on stroke and total mortality.[5] All the patients had atherosclerotic vascular disease, itself a major risk factor for stroke.[5] In the Scandinavian simvastatin survival study (4S), simvastatin treatment (20 to 40 mg daily) reduced the combined incidence of TIA and stroke by 29%.[4] Similarly, in the cholesterol and recurrent events (CARE) trial, pravastatin (40 mg daily) reduced the relative risk of stroke by as much as 32%, over a median follow up period of five years.[147] In the long term intervention with pravastatin in ischaemic disease (LIPID) study, pravastatin (40 mg daily) reduced the relative risk of stroke by 19%.[148] These beneficial effects on stroke and myocardial infarction occur against a background of statins causing a slight increase in circulating Lp(a) values.[35–37] The fact that statins do not reduce Lp(a) concentrations supports the concept that the LDL receptor does not play an important part in the catabolism of Lp(a).[26]

FIBRATES

Fibric acid derivatives exert as favourable an effect on HDL and TG concentrations as on LDL quantity and quality. These drugs also reduce fibrinogen and possibly Lp(a) values.[33] [34] It is tempting to speculate that the favourable clinical end points observed in two recently presented fibrate based clinical trials might be attributable, at least in part, to these beneficial actions. Thus, in the bezafibrate infarction prevention study (BIP), a reduction in the highest fibrinogen concentrations was associated with a decrease in the incidence of the primary end points: cardiac death and ischaemic stroke.[149] Unfortunately, serum Lp(a) values were not monitored. In BIP, there was a very small reduction (6.5 %) in serum LDL values. This reduction in LDL would not be expected to account for the results of this trial. However, because the clinical benefit was limited to patients with raised TG (with or without reduced concentrations of HDL) it is possible that this effect is related to a pronounced rise in HDL and fall in TG values. Another possibility is a fibrate induced reduction in oxidised LDL production because this form of LDL is highly atherogenic. The results of BIP are supported by those of the veterans affairs HDL intervention trial (VA-HIT). In this trial[150], gemfibrozil (1200 mg daily) reduced total reported stroke from 6.9% in the placebo group to 5.1% (p = 0.05) in the treated group. TIA in the same trial were reduced from 4.2% to 1.7% (p = 0.001), and carotid endarterectomy was significantly (p = 0.001) reduced (gemfibrozil, 1.3%; placebo, 3.5%); LDL values were essentially unchanged.

DIABETES, ANTIHYPERTENSIVE DRUGS, AND HORMONAL TREATMENT

Optimising body weight and tight glycaemic control may beneficially influence Lp(a) values in patients with type 1 and type 2 diabetes.[151] This effect is in part linked to TG metabolism, which is impaired in type 2 diabetes, as well as the glycosylation of Lp(a), which interferes with its catabolism.[151] In this setting, it has been shown that treating dyslipidaemia in patients with diabetes (for example, by using a fibrate) improves the lipid profile and lowers the incidence of IHD.[152]

Antihypertensive agents can affect plasma fibrinogen and Lp(a) values as well as the lipid profile.[153] These additional properties might influence the choice of medication, especially in patients where these predictors of vascular events (including stroke) are raised.[153]

Hormonal replacement therapy (HRT) in postmenopausal women is probably associated with a reduction in the risk of developing coronary artery disease.[154]. HRT favourably affects cholesterol, Lp(a), and homocysteine concentrations, especially in those women with the highest concentrations of these risk factors.[155] Several, but not all, studies showed that thyroid replacement treatment decreases Lp(a) concentrations, probably because of an effect upon apo(a) production, or possibly Lp(a) assembly.[28]

FUTURE "THERAPEUTIC" DIRECTIONS

Lp(a) undergoes further modifications after entry into the arterial wall. Whether these changes influence cardiovascular risk or are mere epiphenomena is yet to be determined. However, post-translational events (such as oxidation and proteolysis) could become potential targets for therapeutic intervention.[26]

Any reliable evaluation of a therapeutic intervention to reduce Lp(a) values must rely on a reproducible and standardised assay with appropriate calibration and data analysis appropriate to a highly skewed variable. At present, this objective has not been completely achieved.[26] Initial studies involving Lp(a) measurement may have used even less reliable assays.[53] Clearly, this assay problem is relevant to epidemiological studies. It might also be appropriate to convert data for LDL for the quantity incorporated into Lp(a) molecules. This amount might not be trivial in patients with high Lp(a) concentrations.

Studies assessing the risk attributed to Lp(a) must consider the contribution of other predictors of vascular events (such as hypertension, dyslipidaemia, fibrinogen, and homocysteine).[63] [76] [83] [84] [87] [156]

Concluding remarks

The evidence that Lp(a) is a strong predictor for ischaemic stroke is contradictory. Apart from the lack of universally accepted, standardised methods for determination, Hobbs and White proposed several factors that might contribute to the existing confusion in attributing risk to Lp(a).[53] These include: (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.[53] 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.[53]

The determination of apo(a) isoforms in epidemiological surveys (especially prospective studies), although expensive, might be necessary to define the risk load attributable to Lp(a). Consideration of other risk factors that might be related to plasma Lp(a) values (for example, fibrinogen), or act synergistically with Lp(a) (for example, LDL), will be mandatory in these studies. The genetic and environmental factors controlling the circulating concentrations of Lp(a) also need further definition. Our understanding of the vascular pathology of Lp(a) remains relatively poor.

Reducing the circulating values of Lp(a) might prove difficult. One approach is to deal aggressively with all the other modifiable risk factors.

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