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Lipids and Cerebrovascular Disease: Research and Practice

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Introduction

The relationship between lipids and stroke is complex. In most epidemiological cohorts, there is a direct relationship between cholesterol levels and ischemic stroke. The relationship of lipids to ischemic stroke, however, varies by stroke subtype, with associations strongest for atherosclerotic subtypes. Conversely, there is an increased risk of intracerebral hemorrhage (ICH) at low cholesterol levels, and there is evidence that small vessel disease may share a similar profile of inverse association with lipid levels. The associations also depend on the specific lipid component considered, with the data strongest for total cholesterol and low-density lipoprotein cholesterol (LDL). Given the availability of increasingly potent lipid-lowering agents, understanding the relationship between dyslipidemia and stroke may improve primary and secondary stroke prevention strategies.

Here we review the literature on the relationship between dyslipidemia and stroke, with a focus on lipid screening recommendations and evidence-based approaches to management.

Lipid parameters and stroke risk

Total and LDL Cholesterol

In most, but not all, observational studies, there is an association between higher total and LDL cholesterol levels and increased ischemic stroke risk (Table 1).[1-6]

In addition, most observational studies also found an association between *lower* TC and LDL cholesterol levels and increased risk of hemorrhagic stroke (Table 2).[2, 13-15]

A recent meta-analysis of 23 studies showed an inverse dose-response association between TC and hemorrhagic stroke (OR 0.85 per 1 mmol/L increment, 95% confidence interval

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(95%CI) 0.80-0.91).[18] The mechanism of this association remains unclear. Some studies, however, have shown low serum LDL cholesterol levels in patients with liver disease[19] and hematological malignancies[20] who are at a higher risk of intracerebral hemorrhage. This hypothesis can be tested in large population based cohorts.

Overall, epidemiological studies suggest competing stroke risk related to total cholesterol levels in the general population; high TC is associated with higher risk of ischemic stroke, whereas lower levels are associated with higher risk of brain hemorrhage. Present data do not permit specification of an acceptable cholesterol threshold with regard to these competing risks in either men or women, however.

HDL Cholesterol and HDL subfractions

In some studies, there is an inverse relationship between high-density lipoprotein cholesterol (HDL) and stroke (Table 1).[5, 7, 8] A systematic review of 10 prospective studies found a decreased risk of ischemic stroke ranging from 11 to 15% for each 10 mg/dl increase in HDL cholesterol.[21]

Because studies of the association between HDL cholesterol and stroke yielded mixed results, and recent evidence showed no benefit of HDL-increasing medications on ischemic stroke risk[22], some suggest that the relationship between HDL and cerebrovascular disease is a function of HDL cholesterol sub-fractions rather than of total HDL cholesterol. HDL has two main sub-fractions: larger and less dense HDL (HDL2) and smaller and denser HDL (HDL3) cholesterol. These sub-fractions differ in their biological activity, biochemical properties, and vascular metabolism. HDL3, more so than HDL2, appears to inhibit LDL oxidation and protect against atherosclerosis by its action on the vascular endothelium.

In the Northern Manhattan Study (NOMAS), HDL subfractions had differential effects on the risk of carotid disease; there was a direct relationship between HDL2 and plaque thickness and an inverse relationship between HDL3 and plaque area.[23] In a nested prospective case-control analysis from the Circulatory Risk in Community Study, small and medium size HDL particles were associated with reduced risk of ischemic stroke, in particular lacunar infarcts, and ICH, whereas HDL2 was not associated with stroke risk.[24] More studies are needed to better understand the relationship of HDL subfractions and stroke risk.

Triglycerides

Epidemiological studies evaluating triglycerides (TG) and ischemic stroke also show mixed results, partly due to differential use of both fasting and non-fasting levels (Table 1).[5, 11, 12] In addition, in a meta-analysis of 64 studies, there was an association between higher triglyceride levels and relative risk of stroke (adjusted RR 1.05, 95%CI, 1.03 to 1.07) for each 10 mg/dl increase in baseline TG; fasting and non-fasting status were not specified.[25] Studies have also shown that TG levels are inversely associated with hemorrhagic stroke risk (Table 2).[16, 17]

Lipoprotein (a)

Lipoprotein (a) [Lp(a)] has been identified as an emerging risk factor for cardiovascular disease. Plasma levels of Lp(a) are influenced by genetic factors, with substantial differences across ethnic groups, with levels being highest among African-Americans.[26] Studies on the relationship between Lp(a) and risk of ischemic stroke yielded mixed results. In a nested case-control study of 15,000 healthy predominantly white middle-aged physicians, Lp(a) levels were not associated with stroke risk.[27] In a European cohort, plasma Lp(a) levels also were not associated with ischemic stroke.[28] In ARIC, Lp(a) levels ≥30 mg/mL were associated with increased risk of ischemic stroke in blacks and white women, but not in white men.[29] In a NOMAS case-control study, Lp(a) levels ≥ 30 mg/dl at baseline were associated with an increased risk of ischemic stroke. This association was more pronounced among men and blacks.[30] The effects of Lp(a), therefore, may depend on race-ethnic and other demographic factors, but more research is needed.

Lipids and Ischemic Stroke Subtypes

Some of the discrepant results among observational studies of lipids and stroke risk may be explained by the differential association with ischemic stroke subtypes: there is a stronger association between lipids and strokes due to large artery atherosclerosis. In a case-control study, the association between cholesterol and ischemic stroke risk was strongest for large artery atherosclerosis (OR=3.2).[31] The association between dyslipidemia and large artery atherosclerotic stroke subtype was also shown in other studies. [32, 33]

On the other hand, not all studies showed an association between dyslipidemia and lacunar stroke. In case-control studies, there have been associations between levels of TC[31] and LDL[34] with lacunar stroke. Other studies, however, did not show an association between dyslipidemia and lacunar stroke.[32, 33] Thus the relationship between dyslipidemia and lacunar stroke is complex and likely influenced by genetic and demographic factors in different patient populations, as well as differences in defining stroke subtypes.

While dyslipidemia is a risk factor for coronary heart disease, most studies showed no association between dyslipidemia and embolic stroke.[31, 32,33]

Lipids, white matter disease, and cerebral microbleeds

White matter hyperintensity (WMH), or leukoariosis, has been associated with stroke risk factors including age, hypertension, and smoking.[35] Since WMH, cerebral microbleeds (CMBs), and deep intracerebral hemorrhages are often considered different manifestations of small vessel disease, the relationship between lipids and each of WMH and cerebral microbleeds may help explain the relationship of lipids to small vessel disease. In fact, studies have shown an inverse relationship between dyslipidemia and both WMH[36, 37] and CMBs[38], providing evidence that lower lipid levels may impair small vessel structure or function.

Taken together, the above data provides some evidence of the inverse association between small vessel disease (WMH and CMBs) and hyperlipidemia. This may relate to the role that cholesterol plays in the architecture and integrity of the normal endothelium of small

vessels; thus low lipid levels may interfere with the integrity of the endothelium, or impair endothelial reparative processes, causing “leakage” or obstruction of the small vessels. The exact mechanism remains uncertain and more studies are needed to better characterize the mechanism of this association.

Screening for lipid levels after stroke

In patients with ischemic stroke, a serum lipid profile including TC, LDL, HDL, and triglycerides should be performed.[39] On the other hand, given the scarcity of evidence, routine testing for other lipid components such as Lp(a) and HDL subfractions is not recommended.

The LDL cholesterol usually reported in the lipid profile is generally calculated using the Friedewald formula:

$$\text{LDL Cholesterol} = TC - (\text{VLDL cholesterol} + \text{HDL- Cholesterol}).^{40}$$

This formula is more accurate in the fasting state, since in non-fasting patients post-prandial chylomicrons may contribute to total cholesterol levels and make the measurement less accurate. In addition, this method is inaccurate when the triglyceride level is ≥ 400 mg/dL and has a higher error margin when the LDL is ≤ 70 mg/dL.[41] Direct assays have been developed to measure cholesterol level. Although direct assays are much more expensive than using the Friedwald formula, they may be needed to give an accurate LDL level in certain cases, such as when the TG level is ≥ 400 mg/dL.. Most clinical trials and lipid management guidelines were based on the estimated LDL level, however.

The timing of lipid measurements after stroke may be less important than after myocardial infarction (MI). There is evidence that lipid levels after stroke do not decline as markedly as after MI.[42] In a meta-analysis of 68 studies that included over 300,000 patients, moreover, the association between lipid components and ischemic stroke persisted even when measured in non-fasting patients.[43] As noted above, associations with triglycerides were even more prominent in the non-fasting state. Therefore, while the lipid profile is preferably measured fasting, it can probably be tested even in the non-fasting state,[44] and at any time after the stroke, and should include at least TC, LDL, and HDL cholesterol levels.

Lipid lowering therapy and stroke

Statin therapy in primary stroke prevention

In addition to their cardiovascular benefits, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors have demonstrated efficacy in reducing stroke risk. In primary stroke prevention trials, several statins have been associated with reductions in risk of stroke ranging from 11-40%. The Heart Protection Study (HPS) randomized over 20,000 patients aged 40-80 years with high risk of vascular disease to simvastatin 40 mg daily versus placebo. There was a 25% reduction in stroke risk without an increase in the risk of hemorrhagic stroke.[45] More aggressive treatment was associated with a further reduction in risk. In the Treating to New Targets (TNT) study, compared to atorvastatin 10 mg daily,

atorvastatin 80 mg daily was associated with a 25% reduction in stroke risk that correlated with reductions in LDL. Furthermore, meta-analyses of lipid therapy and stroke showed that with each 1 mmol/L reduction in LDL cholesterol, there was an approximate 20% relative risk reduction in ischemic stroke.[46, 47]

Statin therapy in secondary stroke prevention

A post-hoc analysis of the HPS study showed that in the 3280 patients with a history of cerebrovascular disease without coronary disease, simvastatin treatment was associated with a 5% reduction in the risk of major cardiovascular events or death when compared to placebo.[45] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, however, provides the most direct evidence regarding the role of statins in secondary stroke prevention. SPARCL randomized 4731patients with stroke or TIA and baseline LDL 100-190 mg/dL to atorvastatin 80 mg versus placebo beginning 1-6 months after their event. Over a median follow up of 5 years, atorvastatin was associated with an approximately 2% absolute reduction in recurrent total stroke risk (13.1% vs. 11.2%), with a relative risk reduction of 16%.[48] The benefits of statins on risk reduction were similar across subtypes of the index stroke subtype as well, implying that all ischemic stroke patients, regardless of subtype, should receive statin therapy. Current professional society guidelines, however, reflect a slightly more conservative approach, recommending statin therapy with intensive lipid-lowering effects (i.e., reduces LDL by ≥50%) for patients with ischemic stroke or TIA presumed to be of atherosclerotic origin.[39] The guidelines do recommend treatment for stroke patients with LDL levels below 100 mg/dL, however, which is even lower than the criteria for inclusion in SPARCL, reflecting both the recognition that stroke patients have a similar high risk of future cardiovascular events as patients with other forms of atherosclerotic disease and that use of statin therapy should be based on overall risk rather than only on lipid levels.[49]

SPARCL is the first clinical trial to prove the benefit of high dose statin therapy in secondary stroke prevention, but the effect was modest with a number needed to treat of 50 over 5 years. SPARCL had several limitations, however. For instance, patients were randomized at 1-6 months after stroke, the period where the risk of stroke recurrence falls, especially in patients with large artery atherosclerosis in whom statins may provide the most stroke prevention benefit. Ongoing trials are addressing the role of statin therapy given immediately after stroke, not only to reduce lipid levels and prevent recurrent stroke, but also to ameliorate cerebral injury related to the stroke itself. For example, the Neuroprotection with Statin Therapy for Acute Recovery (NeuSTART) trial is a Phase II trial randomizing patients with acute ischemic stroke to lovastatin 640 mg daily for three days versus placebo to determine the safety and efficacy of lovastatin in reducing infarct size and promoting stroke recovery, which may be a function of the pleiotropic effects of statins.[50] In addition, SPARCL did not establish a target LDL.

Statins Therapy beyond Lipid Control

Investigators suggest that a beneficial “pleiotropic” effect of statins could be through mechanisms different than action on cholesterol metabolism in the liver. These other potential mechanisms include inhibition of the inflammatory cascade, antioxidant effects,

upregulation of nitric oxide synthase (NOS) with consequent increase in cerebral blood flow, plaque stabilization, and modulating coagulation and platelet function. These mechanisms not only have stroke prevention implications, but may also contribute to improved functional outcome in acute ischemic stroke.

Other lipid lowering drugs in stroke prevention

The benefit of non-statin lipid lowering agents for primary or secondary stroke prevention is not as well-established. While niacin increases HDL levels, its benefit in reducing the risk of cerebrovascular events remains uncertain. A meta-analysis of 11 studies (n=9959 subjects) showed no association between the use of niacin and the risk of stroke (OR 0.88, 95%CI 0.50-1.54).[51]

Fibric acid derivatives can also be used to lower triglycerides and increase HDL cholesterol levels, but their efficacy in reducing incident stroke is uncertain. The Veterans Affairs-HDL Intervention Trial (VA-HIT) among men with coronary artery disease and low HDL cholesterol, benzofibrate provided a 31% reduction in stroke risk (p=0.036).[52] A recent meta-analysis, however, that included 18 trials and over 45,000 patients provided no evidence that fibrates reduce stroke risk (RR reduction –3%, 95%CI –16 to 9%).53

Ezetimibe inhibits the intestinal absorption of cholesterol, reducing total cholesterol levels. The recently published IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that the addition of ezetimibe 10 mg daily to simvastatin 40 mg daily resulted in a significant reduction in stroke risk (HR 0.86, 95%CI 0.73-1.00).[54]

A meta-analysis that included 78 trials of lipid-lowering agents showed no significant stroke risk reduction of non-statin lipid lowering interventions including fibrates, other treatments, and diet (OR 0.92, 95%CI 0.69–1.23).[55]

Novel lipid lowering drugs

Proprotein convertase subtilisin-kexin type 9 (PCSK9) is a hepatic protease that degrades hepatic LDL receptors leading to increased serum LDL cholesterol levels. Monoclonal antibody inhibitors of PCSK9 are novel parenterally administered lipid lowering agents that have been shown to reduce LDL by 60-70 percent when added to statin therapy.[56] A meta-analysis of 24 randomized trials including over 10,000 subjects using PCSK9 inhibitors found a significant reduction in all-cause mortality (OR 0.45, 95% CI 0.23-0.86) and MI (OR 0.49, CI 0.26-0.93).[57] In addition, a phase III study showed that alirocumab, one of the PCSK9 inhibitors, was associated with a 62% reduction in LDL, and this translated into a 48% decrease risk of major cardiovascular events. However, there was no difference in stroke risk between the treatment and control groups (0.6% vs. 0.3%, p=0.35), though the stroke risk was low. Some adverse events, including myalgias, injection site reactions, ophthalmologic events, and neurocognitive events (including memory impairment and confusional state), occurred more often in patients receiving alirocumab.[58] The mechanisms of cognitive changes are uncertain, but could reflect changes in white matter integrity in the setting of extremely low LDL levels. Evolocumab is another monoclonal antibody that inhibits PCSK9 that has been shown in a randomized open trial (n=4465 patients) to be superior to standard of care (70 percent of which included statin therapy) in reducing

cardiovascular events over a median follow up of 11.1 months (HR 0.47, 95% CI 0.28-0.78) with the similar overall serious adverse event profile (7.5 percent in each group). More patients on evolocumab had neurocognitive deficits (0.9 vs. 0.3 percent), however.[59] These monoclonal antibodies are currently approved by the FDA, but their use may be challenged by the need for injections. Randomized trials are needed to prove the safety and efficacy of alirocumab and other PCSK9 inhibitors as an add-on treatment to statins in patients with elevated LDL for primary and secondary stroke prevention, particularly in light of the potential for neurocognitive effects.

Statins and intracerebral hemorrhage

While evidence suggests an inverse relationship between lipids and hemorrhagic stroke, the association between statin use and ICH remains unclear. The HPS study was the first clinical trial to show a non-significant increase in the risk of ICH with simvastatin vs. placebo (1.3% vs. 0.7%).[45] In SPARCL, patients on atorvastatin were more likely to have ICH than those on placebo (2.3% vs. 1.4%, p = 0.01).[48] A recent meta-analysis including 31clinical trials, however, showed no increase in risk of ICH with statin use (OR 1.08, 95% CI 0.88-1.32).[60] Any potential increase in risk of ICH is likely to be low, therefore.

Guidelines on Lipid Management

The most recent American Heart Association/American Stroke Association guidelines recommend high-intensity statin therapy for patients with ischemic stroke presumed to be related to atherosclerosis, regardless of LDL level. High intensity statin therapy is defined as therapy sufficient to lower the LDL-C by at least 50%; no specific target values are provided any longer. The guidelines further recommend that use of statin therapy in patients with non-atherosclerotic mechanisms should be based on their overall cardiovascular risk and comorbid conditions.[39] This is also based on the American College of Cardiology/American Heart Association guidelines that move away from reliance on LDL levels to determine the intensity of statin therapy.[44] According to these guidelines, statin therapy is recommended to patients with (1) clinical atherosclerotic cardiovascular disease (ASCVD) (atherosclerotic stroke or TIA and coronary artery disease); (2) LDL cholesterol ≥ 190 mg/dL; (3) age 40-75 years, diabetes, and LDL cholesterol 70-189 mg/dL; (4) LDL cholesterol 70-189 mg/dL, no diabetes, and estimated 10-year ASCVD risk of ≥ 7.5% based on the new pooled cohort equations. High intensity statin therapy is recommended for those ≤ 75 years and at low risk of statin complications, with ASCVD, LDL cholesterol ≥ 190 mg/dL, or DM and a 10-year risk of ASCVD of ≥7.5%. Moderate intensity statin therapy (i.e., a lowering of LDL-C of 30-50%) is recommended for other groups.

Conclusion

Lipids have a complex relationship with cerebrovascular disease. There is a direct relationship between cholesterol levels and ischemic stroke, and particularly atherosclerotic disease, and the associations are strongest for total cholesterol and LDL. There is an increased risk of ICH at low cholesterol levels, and there is evidence that low lipid levels also increase the risk of small vessel disease. Statins reduce the risk of recurrent stroke after

ischemic stroke, but the role of adding newer lipid lowering agents remains to be determined.

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Table 1

Lipid profile component and ischemic stroke risk

Lipid Profile component	Study	Characteristics	Results
Total Cholesterol	Alpha-Tocopherol, Beta Carotene Cancer Prevention Study[1]	28,000 men smokers	Increased risk of ischemic stroke with a total cholesterol levels 7 mmol/L or greater (≥ 271 mg/dL) (HR 1.25 95% CI 0.99 – 1.57)
	Asia Pacific Cohort Studies Collaboration[2]	352,033 individuals from Asia and New Zealand	For every 1 mmol/L increase in total cholesterol, there was a 25% (95% CI 13 to 40%) increase in ischemic stroke rate
	Women's Health Study[3]	Prospective cohort study of 27,937 US women aged ≥ 45 years	Total cholesterol level was associated with ischemic stroke (adjusted HR per 1 mmol/L increase for ischemic stroke of 1.17 (95% CI, 1.06-1.30)
	Eurostroke Project[4]	22,183 subjects	No relationship between total cholesterol level and ischemic stroke.
	Women's Pooling Project[6]	24,343 US women <55 years of age with no previous cardiovascular disease	Higher total cholesterol was associated with increased risk of ischemic stroke (HR 1.69 95% CI 0.91-3.13, for top-most quintile compared with the lower-most one)
LDL Cholesterol	Women's Health Study[3]	Prospective cohort study of 27,937 US women aged ≥ 45 years	Serum LDL cholesterol was associated with increased risk of ischemic stroke [HR 1.74 95% CI 1.14, 2.66; p(trend across quintiles) = 0.003]
	The Atherosclerosis Risk in Communities (ARIC)[5]	14,175 middle-aged men and women without clinical cardiovascular disease	Non-significant association between LDL cholesterol and ischemic stroke (HR 1.26 95% CI 0.91-1.76, for top-most quintile compared with the lower-most one)
HDL Cholesterol	Copenhagen City Heart Study[7]	19,698 women and men at least 20 years old	47% reduction in the risk of non-hemorrhagic stroke for every 1 mmol/L increase in HDL.
	Northern Manhattan Stroke Study (NOMASS) [8]	539 patients and 905 controls	Inverse relationship between ischemic stroke and HDL level ≤ 35 mg/dL (0.91 mmol/L) (OR 0.53; 95% CI, 0.39-0.72).
	Cardiovascular Health Study[9]	5,201 adults aged 65 and older living in U.S. communities, plus a recruitment of 687 African Americans 3 years later.	Higher HDL cholesterol level was associated with a decreased risk of ischemic stroke in men, but not in women
	The Atherosclerosis Risk in Communities (ARIC) [5]	14,175 middle-aged men and women without clinical cardiovascular disease	No relationship between HDL cholesterol and ischemic stroke in men and a non-significant association in women.
Triglycerides	The Atherosclerosis Risk in Communities (ARIC) [5]	14,175 middle-aged men and women without clinical cardiovascular disease	Fasting triglyceride levels were not associated with ischemic stroke
	Physicians' Health Study[10]	Men, 296 strokes and 296 controls	No association between triglyceride level and ischemic stroke
	Copenhagen City Heart Study[11]	prospective, population-based cohort study comprising approximately 14 000 persons	15% (95% CI 9 to 22%) increased risk of ischemic stroke for each 89 mg/dl increase in nonfasting triglycerides.
	Women's Health Study[12]	Prospective cohort study of 27,937 US women aged ≥ 45 years	The highest tertile of non-fasting but not fasting Triglyceride level was associated with increased ischemic stroke risk when compared to lowest tertile.

Table 2

Lipid profile component and hemorrhagic stroke risk

Lipid Profile component	Study	Characteristics	Results
Total Cholesterol	Multiple Risk Factor Intervention Trial (MRFIT)[13]	Over 350 000 men	Three-fold increase in the risk of fatal intracerebral hemorrhage in patients total serum cholesterol (TC) <4.13 mmol/L when compared to those with values ≥ 4.13 mmol/L
	Asia Pacific Cohort Studies Collaboration[2]	352,033 individuals from Asia and New Zealand	For every 1 mmol/L (38.7 mg/dL) increase in total cholesterol, there was a 20% (95% CI 8 to 30%) reduction in the risk of hemorrhagic stroke
	Korean Medical Insurance Corporation Study[14]	115,000 men	Low serum cholesterol was not associated with intracerebral hemorrhage
LDL Cholesterol	Pooled cohort analysis of the ARIC study and the Cardiovascular Health Study (CHS)[15]	Over 263 489 person-years of follow-up	LDL was inversely associated with hemorrhagic stroke risk (HR for topmost quartile versus lowest 3 quartiles 0.52 95% CI 0.31-0.88)
Triglycerides	Three City Study[16]	8393 men and women aged 65 years old or older	A triglycerides level ≤ 0.94 mmol/L was associated with an increased risk of hemorrhagic stroke (adjusted HR 2.35 95% CI 1.18-4.70)
	Rotterdam study[17]	over 9 000 subjects aged 55 years or older	The highest quartile of Triglyceride level had a lower risk of intracerebral hemorrhage when compared to the lowest quartile (HR 0.20 95% CI 0.06-0.69)