High-Density Lipoprotein Cholesterol
An Emerging Target for Stroke Treatment

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Background and Purpose—This review characterizes the current state of knowledge of high-density lipoprotein (HDL) in relation to stroke.

Summary of Review—HDL has anti-atherosclerotic and anti-inflammatory properties and is an important component in atherosclerosis. Serum HDL-cholesterol levels are inversely related to heart disease and stroke risk. There are various established and experimental treatments which can raise serum HDL cholesterol and improve its function.

Conclusion—HDL is an emerging target for atherosclerotic stroke treatment with the potential to dramatically impact the care of stroke patients. (Stroke. 2007;38:1104-1109.)

Key Words: cholesterol ■ lipids & lipoprotein ■ stroke

Atherothrombosis is the leading cause of death worldwide through its manifestations as ischemic heart and cerebrovascular disease. Although several therapies that specifically target atherosclerotic disease have been shown in clinical trials to lower the risk of vascular events including stroke, it is clear that additional therapeutic options that can mitigate the burden of vascular disease on society need to be identified.

One such potential therapeutic option may be boosting the concentration or enhancing the function of high-density lipoprotein cholesterol (HDL). HDL is intimately involved in atherosclerosis and is a promising target for risk-modifying interventions aimed at limiting vascular disease. This review characterizes the current state of knowledge about HDL, including its structure, function, and diagnostic tests, its contribution to cerebrovascular disease, and its potential role as a therapeutic target to modify vascular risk in stroke patients.

HDL: Structure and Function
Lipoproteins are complexes of proteins, phospholipids and cholesterol. HDL is the smallest and densest of the lipoproteins because of its high protein content. Proteins make up about 50% of its mass and apolipoprotein A-I (apoA-I) accounts for 70% of that protein component.

ApoA-I is a 243 amino acid protein synthesized in the liver (70%) and intestine (30%) and secreted into the serum in a lipid-free state. Individual apoA-I molecules associate with other apoA-I molecules, membrane phospholipids and cholesterol to form lipid-poor pre-β-HDL. Lipid-poor HDL assumes a double-belt-like structure which becomes spherical with maturation and addition of cholesterol.

Lipid-poor β-HDL is able to take up cholesterol from artery wall macrophages via the ATP-binding cassette A-1 (ABCA-1) receptor. Cholesterol is transferred into lipid poor HDL and is then esterified by the enzyme lecithin-cholesterol acyltransferase. As cholesterol is esterified it is packaged into the core of the HDL leading to formation of the mature spherical lipoprotein.

Mature spherical HDL can then unload its cholesterol by 2 main mechanisms. Transfer of cholesterol back to the liver is facilitated by interaction with the scavenger receptor-B1 (SR-B1) receptor on hepatocytes and leads to formation of bile and secretion into the gut. Alternatively, cholesterol can be transferred from mature HDL to low-density lipoprotein (LDL) or very-low-density lipoprotein (VLDL), a process dependent on cholesteryl ester transfer protein (CETP). This leads to a recycling of cholesterol, potentially back into the artery wall.

Mechanisms of Action
There are several mechanisms by which HDL protects against atherosclerosis, including reverse cholesterol transport, antioxidant effects, anti-inflammatory effects, antithrombotic effects, and modification of endothelial function (Figure).

In reverse cholesterol transport, cholesterol is transported by HDL from the artery wall to the liver for excretion. Cholesterol is removed from macrophages in the subintima of the vessel wall by the interaction of HDL with ABCA-1, SR-B1, or by passive diffusion. Once esterified, cholesterol in the HDL is then transported to the liver for excretion.
In contrast to Vitamin E, a far less potent antioxidant, HDL and apoA-I are able to prevent lipid oxidation, a key mechanism in atherosclerosis in both cell-free and artery-wall coculture studies. HDL is a major carrier of lipid hydroperoxides and paraoxonase, an enzyme involved in preventing and reversing oxidative damage.

HDL blocks inflammation by acting as an antioxidant but also by limiting the expression of cytokines such as tumor necrosis factor–α and interleukin-1 that mediate upregulation of leukocyte endothelial adhesion molecules. This has been demonstrated in cell cultures where monocyte chemotactic activity can be blocked with the addition of normal functioning HDL.

Finally, HDL may also reduce thrombotic risk through the inhibition of platelet activation and aggregation and may improve endothelial function by stimulating prostacyclin release.

**Epidemiology**

In the United States, low HDL (<40 mg/dL) is present in 35% of men and 15% of women. The prevalence of low HDL is expected to rise because of increasing rates of obesity, diabetes, and the metabolic syndrome.

**Serum HDL Cholesterol and Coronary Risk**

The inverse relationship of serum HDL cholesterol (HDL-C) and coronary heart disease (CHD) has been well established in large prospective studies. Gordon and colleagues analyzed the relation between HDL-C and CHD incidence in 4 prospective American studies: the Framingham Heart Study (FHS), the Lipid Research Clinics Prevalence Mortality Follow-up Study, the Lipid Research Clinics Coronary Primary Prevention Trial (CPPT), and the Multiple Risk Factor Intervention Trial (MRFIT). A 1-mg/dL increase in HDL-C was associated with a significant 2% decrease in CHD risk in men (FHS, CPPT, and MRFIT) and a 3% decrease in women (FHS). In the FHS, HDL-C was the most potent lipid risk factor for cardiovascular disease. These findings were confirmed in subsequent studies.

**Serum HDL Cholesterol and Stroke Risk**

The inverse relationship between serum HDL-C and stroke risk has strengthened in light of more recent epidemiological studies. Large cohort studies which have addressed this question (Table 1) included the British cohort, the Honolulu heart program, the Atherosclerosis Risk in Communities (ARIC) study, the Oyabe study, Dubbo study, Copenhagen city heart study and the Israeli Ischemic Heart Disease Study. Although using different HDL levels in comparison, most studies demonstrated a significant inverse association and others demonstrated nonsignificant trends toward an inverse relationship of serum HDL-C and ischemic stroke risk. The populations studied included middle-aged and elderly men and women from America, Australia, Europe, Hawaii, Israel and Japan. When taken together it seems clear that higher baseline levels of serum HDL-C lower the risk of subsequent ischemic stroke. Case-control studies have also demonstrated this inverse relationship.

Low serum HDL-C levels may reflect a greater risk for atherosclerotic stroke, a hypothesis supported by a few case-control studies. A study of 240 consecutive patients with stroke or transient ischemic attack demonstrated that low serum HDL-C levels were more frequently seen in the setting of atherosclerotic large-vessel disease relative to other stroke subtypes, including small-vessel disease. In the NOMASS study of HDL the odds of having an atherosclerotic large-vessel stroke was 0.20 in those with HDL-C concentrations ≥35 (0.08 to 0.5, P<0.001) versus 0.60 (0.42 to 0.85, P<0.01) for other stroke types. Similarly, the Group Health Cooperative study showed that odds of having a large-vessel atherothrombotic stroke was reduced (odds ratio=0.4) in the highest HDL-C quintile when compared with the lowest. The same association was not present for other stroke subtypes.

**TABLE 1. Summary of Trials Evaluating Role of High Density Lipoprotein in Stroke**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Years Followed</th>
<th>Stroke Type</th>
<th>HDL Categories</th>
<th>Adjusted Risk</th>
<th>CI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen</td>
<td>19698</td>
<td>6</td>
<td>Ischemic</td>
<td>1 mmol/L increase</td>
<td>0.53</td>
<td>0.34–0.83</td>
<td>16</td>
</tr>
<tr>
<td>Israeli Ischemic Heart Disease</td>
<td>8586</td>
<td>21</td>
<td>Ischemic</td>
<td>High vs Low Tertile</td>
<td>0.75</td>
<td>0.54–1.05</td>
<td>17</td>
</tr>
<tr>
<td>British Regional Heart</td>
<td>7735</td>
<td>16.8</td>
<td>All</td>
<td>High vs Low Quintile</td>
<td>0.68</td>
<td>0.46–0.99</td>
<td>11</td>
</tr>
<tr>
<td>Dubbo</td>
<td>2805</td>
<td>8.2</td>
<td>Ischemic</td>
<td>1 mmol/L increase</td>
<td>0.64</td>
<td>0.44–0.94</td>
<td>15</td>
</tr>
<tr>
<td>Honolulu Heart Program</td>
<td>2444</td>
<td>6</td>
<td>Ischemic</td>
<td>≥60 vs &lt;40 mg/dl</td>
<td>0.37</td>
<td>0.17–0.83</td>
<td>12</td>
</tr>
<tr>
<td>Atherosclerosis Risk in Communities</td>
<td>14175</td>
<td>10</td>
<td>Ischemic</td>
<td>High vs Low Quartile</td>
<td>0.81</td>
<td>0.54–1.20</td>
<td>13</td>
</tr>
<tr>
<td>Oyabe</td>
<td>4989</td>
<td>10</td>
<td>Ischemic</td>
<td>≥60 vs &lt;30 mg/dl</td>
<td>0.34</td>
<td>0.14–0.85</td>
<td>14</td>
</tr>
</tbody>
</table>
This association of HDL with atherosclerotic stroke is further strengthened by a study of carotid plaque progression.22 In 1952 subjects followed for 7 years, low HDL-C was associated with a significant increase in carotid plaque volume by ultrasound. The association of low HDL with increased plaque volume was strengthened when patients on cholesterol-lowering agents were excluded and may indicate an independent effect of HDL-C.

Few studies have compared serum HDL-C against serum LDL-C to determine relative contributions to stroke risk. In one study of the very old (aged ≥85 years) low serum HDL-C was associated with an increased risk of stroke, cardiovascular disease, and mortality whereas LDL-C and total cholesterol had no association.23 On the other side of the age spectrum, a study of young stroke patients demonstrated that low HDL-C was the only serum lipid index associated with an increased risk of stroke.24

Measuring HDL Function: Better Than HDL-C Levels?

Studies have shown variability among individuals in regards to HDL function. For example, the apoA1milano variant has a prolonged residence time in plasma and improved function conferring protection from atherosclerosis. Variability in HDL function may help explain why some individuals with advanced atherosclerosis have very high HDL-C and why many heart attacks and strokes occur in individuals with normal HDL-C levels. Whereas normal HDL is anti-inflammatory, studies have shown that HDL from some patients with cardiovascular disease is dysfunctional and actually pro-inflammatory.25 Populations at risk of having advanced atherosclerosis have very high HDL-C and why HDL function may help explain why some individuals with cardiovascular disease, and mortality whereas LDL-C and total cholesterol had no association.23 On the other side of the age spectrum, a study of young stroke patients demonstrated that low HDL-C was the only serum lipid index associated with an increased risk of stroke.24

Raising Serum HDL-C

Raising serum HDL-C can decrease cardiovascular risk by 5.5% for each 1 mg/dL increment in baseline HDL-C.33 There are various pharmacological and nonpharmacological means to increase serum HDL-C.34 Lifestyle-associated improvement in HDL-C appear to be greatest in persons with the highest baseline HDL-C levels (≥60 mg/dL).35 Many of these lifestyle modifications have been shown to reduce overall stroke risk, but it is unclear what effect they will have in patients with low-HDL at the highest risk of cardiovascular disease.

Pharmacological Treatments

Fibrates

Fibrates are effective at raising HDL-C level and lowering triglyceride levels and are ligands for peroxisome proliferator-activated receptors (PPARs), nuclear receptors that regulate the expression of genes involved in glucose and lipid metabolism, inflammation, and endothelial function.36 Raising HDL and lowering triglycerides with gemfibrozil has been shown to reduce major cardiovascular events, even in the absence of LDL-lowering.37 The reduction in stroke risk with gemfibrozil treatment was evident after 6 months, and those with the lowest HDL-C at baseline seemed most likely to benefit from treatment.38

Niacin

Niacin doses of 1 to 2 g per day can increase in HDL-C of 20% to 30%. The extended-release (ER) niacin preparation niacin is better tolerated, with fewer flushing episodes and none of the liver toxicity seen with other slow-release preparations. The flushing from niacin is attributable to release of prostaglandin D2. The flushing can be mitigated by several days of pretreatment with aspirin to inhibit formation of prostaglandin D2. Trials of niacin in cardiovascular disease have not evaluated stroke as an independent end point but have shown significant reductions in cardiac end points.39

Statins

Statins have been shown to reduce the risk of ischemic stroke by about 20% in multiple large studies.40 Each 10% reduction in LDL-C is estimated to reduce the risk of stroke by 15.6% (95% CI, 6.7 to 23.6).41 The effects of statin therapy on HDL-C vary based on the particular agent and dose used; for example, high-dose rosuvastatin increased HDL-C by 14% whereas high-dose atorvastatin increased HDL-C by less than 3%.42 A study of in-hospital initiation of statin in stroke patients found no significant effect on HDL-C at 3 months from statin initiation.44 The effect of statins may vary among patients, with those with low HDL-C and elevated triglycerides more likely to benefit from statin therapy.40

Combination Therapy

Combination therapy may hold the key to the most dramatic increase in HDL-C, and combinations of statin and niacin have demonstrated 18% to 21% increase in HDL-C.45,46 The HDL Atherosclerosis Treatment Study (HATS) highlighted the benefits of combining statin therapy with niacin. The combination halted angiographic atherosclerosis progression and reduced major clinical events.45 Data from the
TABLE 2. Promising HDL Therapies Being Studied or Developed

<table>
<thead>
<tr>
<th>Therapies</th>
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<tbody>
<tr>
<td>CETP inhibitors</td>
</tr>
<tr>
<td>ApoA-I peptides</td>
</tr>
<tr>
<td>PPAR agonists</td>
</tr>
<tr>
<td>HDL Delipidation</td>
</tr>
<tr>
<td>Upregulator of the SR-BI receptor</td>
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<tr>
<td>Inhibitors of endothelial lipase</td>
</tr>
<tr>
<td>Vaccine against CETP</td>
</tr>
<tr>
<td>Liver Xα/β agonists</td>
</tr>
<tr>
<td>Gene therapy</td>
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</table>

Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER-2) study demonstrated that ER-niacin added to statin therapy may halt the progression of atherosclerosis, as measured by carotid intima-media thickness among CHD patients with low HDL-C levels. After 1 year of treatment, mean carotid intima-media thickness increased in the statin-only group but not in those treated with ER niacin. The addition of ER-niacin to background statin was well-tolerated with adherence exceeding 90%.47

The National Institutes of Health (NIH) is sponsoring the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial which will evaluate the merits of simultaneously lowering LDL and raising HDL cholesterol levels, in patients randomized to ER-niacin plus simvastatin or to simvastatin alone. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is testing fenofibrate plus a statin versus a statin alone in patients with type 2 diabetes.

Emerging Therapies

Several new agent classes are in development to raise HDL levels (Table 2). Three of the most promising agent classes actively being studied are:

**CETP Inhibitors**

CETP inhibitors block the enzyme that facilitates recirculation of cholesterol via VLDL and LDL. Partial inhibition of this enzyme is associated with an increase of HDL-C by up to 106%. CETP inhibitors may be more effective in combination with statins. Certain side effects, such as an increase in blood pressure, have been noted and clinical trials using the combination of atorvastatin and torcetrapib are underway.

**ApoA-I Peptides**

ApoA-I peptides are agents that improve HDL function by providing one of the substrates to HDL formation. Experimental evidence indicates that both over-expression of the apoA-I gene and direct infusion of apoA-I in animal models increase HDL-C levels and decrease atherosclerosis. The 2 main apoA-I peptides being studied are the apoA-I_Milano complex and the D-4F peptide.

Injection of apoA-I_Milano complex reduced the lipid content and inflammation of atherosclerotic lesions and induced regression of atherosclerosis in animal models. These results have since been replicated in humans. Using intravascular ultrasound, 5 weekly infusions of a recombinant version of apoA-I_Milano produced a modest but significant 4% regression of coronary atherosclerosis in 47 acute coronary syndrome patients.

Short apoA-I mimetic peptides created from D-amino acids such as D-4F have been shown to increase formation of pre-β-HDL acutely. These peptides can be taken orally and have been shown to prevent atherosclerosis and block inflammation in experimental models.

These classes of agents are promising in their ability to acutely boost HDL function in the setting of acute stroke and improve HDL metabolism and function. These agents are currently being tested in early human clinical trials.

**PPAR Agonists**

Large, buoyant HDL particles may be associated with reduced cardiovascular risks. The PPAR agonists, such as the glitazones, are known to have modest HDL-boosting effects although their main action is in reducing insulin resistance. A recent study suggested that pioglitazone increased the size and buoyancy of HDL particles in combination with other diabetic treatments in patients with type 2 diabetes. The percentage distribution of larger HDL particles (HDL 2) increased by 2% to 3% over the 24-week study period, whereas the smaller HDL particles (HDL 3) decreased by 1.5% to 2.5%. The NIH sponsored Insulin Resistance Intervention after Stroke (IRIS) trial is currently looking at the effect of pioglitazone in recent ischemic stroke patients.

**Acute Stroke Therapy**

In addition to targeting chronic HDL elevation as a stroke prevention intervention, acute augmenting of HDL-C is promising as a therapy for acute ischemic stroke. HDL has been shown to reduce neuronal damage after onset of ischemic stroke, possibly by antioxidative/anti-inflammatory mechanisms, in both excitotoxic and middle cerebral artery occlusion models of stroke. Additionally, treatment with apoA-I reduces brain lesion size by 64% in the middle cerebral artery occlusion model. Infusing HDL or apoA-I into humans decreases inflammation, stabilizes plaque and has the potential to improve outcomes. Acute augmentation of HDL by direct infusion or by increasing apoA-I may be a powerful neuroprotective tool acting via multiple mechanisms for the treatment of acute stroke.

High-dose statins are currently being studied in the setting of acute stroke, and one of their mechanisms of action may be in augmentation of HDL. Patients will be treated with very high doses of lovastatin (escalating dosage levels of 1, 3, 6, 8, and 10 mg/kg) for 3 days after acute stroke. Conventional dose lovastatin does increase HDL-C by 6%, and HDL increases may be greater at the planned high dose.

**Conclusions**

Atherosclerotic stroke is the end result of many different pathological processes in which HDL-C is a critical component. It is being increasingly recognized that low HDL-C is an important risk factor that is highly modifiable in relation to atherosclerosis. A strategy of HDL augmentation with the
combination of statins and long-acting niacin may be the best means of raising serum HDL-C at present. However, although it may be reasonable to aim to increase HDL-C, it must be acknowledged that compelling proof of benefit from randomized clinical trials with clinical-event end points is not yet available.

On the basis of available evidence, it would seem reasonable to start all atherosclerotic stroke patients with HDL <40 on the combined statin and long-acting niacin therapy with the goal of increasing HDL by 20%. The future holds the promise of newer HDL-directed therapies with the potential to further boost serum HDL-C concentration and improve HDL-C function.

Disclosures

None.

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