

Management of Lipid Disorders for Stroke Prevention

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Abstract: *Lipid disorders are common among stroke patients, many of whom also have coronary artery disease. Cholesterol, a lipid, plays a major role in the development of plaque and resulting atherosclerosis. Understanding laboratory values, stroke risk, pharmacological management, and lifestyle modifications associated with lipid disorders is critical to improving care for stroke patients with lipid disorders.*

An understanding of cholesterol and management of cholesterol abnormalities is important for prevention of vascular insults. This article reviews plaque development, cholesterol and related components, risks associated with elevated cholesterol levels, management options, complications of pharmacological approaches, and the role of the neuroscience nurse.

Neuroscience nurses often care for stroke patients with comorbidities including atherosclerosis. Atherosclerosis is a disease process of large and medium-sized arteries characterized by endothelial dysfunction, inflammation, and plaque build-up in the intima of the vessel wall. Cholesterol has been implicated in the development of atherosclerosis and, eventually, coronary artery disease (CAD) and stroke.

Plaque Formation

Plaque is a deposit of mostly fatty material within the arterial wall. Plaque formation, a component of atherosclerosis, is a complex process involving the endothelium, cell mediators, oxidized lipoproteins, lymphocytes, and thrombogenic components. Although many theories of plaque formation are still under investigation, accumulating evidence points to inflammation as a key component in the initiation and progression of plaque development and rupture (Farmer & Gotto, 2002).

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A healthy endothelium favors vasodilation, anti-thrombosis, fibrinolysis, and monocyte disadhesion (Gotto & Pownall, 1999). The endothelium produces a number of mediators, such as nitrous oxide, that maintain vascular tone and inhibit thrombus formation. The endothelium also produces tissue plasminogen activator and prostacyclin, both of which are crucial to maintaining an antithrombotic environment. These mediators are activated by increased low-density lipoprotein (LDL) cholesterol levels, hypertension, smoking, homocystinemia, immune complexes, and other infectious agents (Forrester, 2002). Oxidized LDLs cause inflammation and stimulate the production of cell-adhesion molecules and cytokines. Macrophages feast on available LDLs to produce lipid-laden foam cells to form the lipid core of plaque (Gotto & Pownall).

Plaque is nourished through microvessels that grow in the thickened arterial wall. As plaque grows, a fibrous cap formed by migration of smooth muscle cells constantly breaks it down and builds it up. As the thickened lesion expands toward the outer edge of the blood vessel, the shape of the blood vessel changes. This process is known as remodeling. The blood vessel lumen is not impeded until approximately 40% of the circumference is affected and the lesion starts to grow inward.

Evidence of plaque rupture and blood vessel healing is found in lesions that cause ischemic events. Features associated with plaque rupture include a large, soft, thin fibrous cap; inflammation in the fibrous cap and adventitia; and outward vessel remodeling (Shah, 2002). The fibrous cap may tear, break, or disintegrate, allowing blood to come in contact with prothrombogenic contents of the plaque. The rough, ulcerated surface produced by the rupture further stimulates thrombosis. As the thrombosis grows, the intraluminal diameter decreases, causing arterial blockage. Following plaque rupture, fibrinolysis occurs, removing some of the thrombotic material.

Plaque rupture is prevented by decreasing vascular inflammation and enhancing plaque stability and endothelial function. Some medications, such as statins, have the effect of stabilizing plaque, although they do not lower blood lipid levels (Futterman & Lemberg, 1999). This effect is referred to as pleiotropic. Cholesterol-independent neuroprotective properties of statins include enhancement of nitric oxide bioavailability as well as anti-inflammatory, antithrombotic, and antioxidant actions (DiNapoli, Taccardi, Oliver, & DeCaterina, 2002; Moran, 2004).

Cholesterol and Related Components

A lipid is an organic compound, such as a fat, oil, or wax, that is insoluble in water. Cholesterol and triglycerides are the two main blood lipids. Cholesterol is used to form steroid hormones and bile acids. Triglycerides are fat molecules; they are important in transferring energy from food into cells.

High-density lipoproteins (HDLs), known as the good cholesterol, have the ability to move cholesterol away from the arterial wall to the liver. HDLs are made in the liver and intestines.

Low-density lipoproteins (LDLs) contribute to plaque formation and are known as the bad cholesterol. A very low-density lipoprotein (VLDL) consists of triglycerides and other lipids. When the body loses energy, triglycerides become LDLs.

Laboratory Values

Components of the lipid profile include total cholesterol, LDL, HDL, and triglyceride levels. Lipid profiles are more reflective of clinical condition if the person fasted for 12 hours before the blood sample was drawn. Total and HDL cholesterol values are accurate when drawn from a person in a nonfasting state (Wittert, 2004a). If the lab values for a specimen obtained from a nonfasting person are abnormal, it is recommended that the test be repeated after the patient has fasted for 12 hours (Learelle, 2001). If triglyceride levels are <400 mg/dl, the LDL level cannot be calculated, because the formula used is valid only if triglycerides are <400 mg/dl (Learelle). A direct LDL test may be performed as an alternative in this situation.

According to the National Cholesterol Education Program Adult Treatment Panel (ATP) guidelines (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), a baseline blood lipid value should be obtained for all men and women at the age of 20 years and every 5 years thereafter. Blood lipid level ranges are delineated in Table 1.

Medications such as steroids, progestins, retinoids, thiazide diuretics, and beta blockers can affect serum lipid levels (Mayo Clinic, 2006; Merck & Co., Inc., 2006). For example, corticosteroids raise HDL, LDL, cholesterol, and triglyceride levels (Boots, Christiaans, & van Hooff, 2004). Thiazide and loop diuretics have been shown to increase cholesterol, LDL, and triglyceride levels. Beta blockers increase triglycerides and decrease HDLs (Mantel-Teeuwisse et al., 2001).

Risk for Vascular Events

It is known that HDLs have an antiatherogenic effect (Toth, 2004). High HDL levels have been associated with longevity and protection from vascular events such as myocardial infarction and stroke. In a British study, higher HDL levels were associated with a significant decrease in nonfatal stroke in men with no

Table 1. Adult Treatment Panel III Classification of LDL, HDL, and Total Cholesterol

LDL cholesterol	
<100 mg/dl	Optimal
100–129 mg/dl	Near optimal/above optimal
130–159 mg/dl	Borderline high
160–189 mg/dl	High
≥190 mg/dl	Very high
HDL cholesterol	
<40 mg/dl	Low
≥60 mg/dl	High (desirable)
Total cholesterol	
<200 mg/dl	Desirable
200–239 mg/dl	Borderline high
≥240 mg/dl	High

From "Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), by Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001, Journal of the American Medical Association, 285, 2486–2497.

stroke history ($N = 7,683$; Wannamethee, Shaper, & Ebrahim, 2000). Conversely, low HDL levels (less than 40 mg/dl) were associated with increased CAD risk. Low HDL levels are considered a marker for hypertriglyceridemia and elevated remnant particle concentrations (Expert Panel, 2001; Toth).

Wittert (2004a) summarized the following key points about cholesterol values and related risk:

- The higher the total cholesterol and LDL levels, the higher the risk of CAD
- The higher the HDL level, the more protection one receives against CAD
- High triglyceride levels are an independent risk factor for CAD
- Low HDL levels are also an independent risk predictor of CAD.

Treatment Strategies

Experts who developed the ATP III guidelines recommend targeting high LDL levels (2001). The optimal LDL level is <100 mg/dl; >190 mg/dl is considered very high (McDonald, 2003). Oxidized LDLs impair endothelial-dependent vasodilation, induce apoptosis of endothelial cells, generate an inflammatory response, inhibit nitric oxide activity on platelets, and modify the functional response of vascular smooth muscle (Futerman & Lemberg, 1999).

ATP III guidelines are congruent with the American Diabetes Association guidelines that advocate decreasing LDL levels and, secondly, increasing HDL levels. The target for HDL levels has not yet been identified (Toth, 2004). Low HDL levels are associated with

increasing obesity, metabolic syndrome, and diabetes mellitus (Toth).

Medications

Statins

Five general categories of medications are available for the treatment of lipid disorders (Table 2). Statins are cholesterol-lowering drugs that work by stimulating hepatic lipoprotein A-1 expression and weakly inhibiting the cholesterylester transfer protein (CETP), which changes HDLs to LDLs (Toth, 2004). People with low HDL levels benefit most from statins (Toth). Statins may also decrease stroke risk by lowering systolic and diastolic blood pressures (Amarenco, Labreuche, Lavalley, & Touboul, 2004).

The first statin developed was lovastatin (Mevacor); six statins are presently marketed in the United States. There are two types of statins: fermentation-derived natural statins, (e.g., lovastatin) or synthetic statins (e.g., atorvastatin and fluvastatin). The naturally derived statins have shown the greatest benefit in decreasing stroke and CAD incidence (Futterman & Lemberg, 1999).

Numerous studies and meta-analyses have concluded that cholesterol-lowering medications reduce stroke risk for patients with known CAD and normal or elevated cholesterol levels but not for patients with a history of stroke or transient ischemic attack (TIA; Futterman & Lemberg, 2004; Lockman, Tribastone, Knight, & Franko, 2005). The American Stroke Association Stroke Council (2004) has stated that, "given early benefits in trials of acute coronary syndromes, statin initiation during hospitalization for first ischemic stroke of atherosclerotic origin is probably justified and may increase rates of long-term use" (2004, p. 1023).

Individuals who take statins for long periods of time are most at risk for complications. All statins have the potential to cause muscle problems, but based on clinical trials, muscle symptoms attributed to statins are rare (Moran, 2004). The mechanism by which statins cause muscle problems remains unknown, although a number of theories have been proposed (Thompson, Clarkson, & Karas, 2003). A lower cholesterol level within the muscles may lead to muscle instability. Statins may block small proteins that help maintain the stability of the muscle cell membrane. It also is postulated that there may be a decrease in a compound involved in mitochondrial transport. Use of more than one statin at a time is not recommended because of the increased risk of muscle problems (Moran).

The spectrum of muscle complaints ranges from myalgia to rhabdomyolysis, with or without elevations in creatine kinase (CK; Moran, 2004). Myopathy is muscle pain or weakness associated with grossly elevated CK (more than 10 times the normal upper limit; Thompson et al., 2003). Although routine measurement of CK levels

in asymptomatic patients is not required, a baseline CK measurement is recommended (Thompson et al.; Wittert, 2004b). CK levels less than 5 times higher than normal do not require intervention, but muscle pains require further investigation and possible treatment. CK levels 5–10 times higher than normal need to be monitored closely. CK levels higher than 10 times normal warrant dose reduction (Moran, 2004).

A hepatic panel should be done at baseline, with the patient fasting. This panel should be repeated 6–12 weeks after initiation of statin therapy, 6 months later, and periodically afterwards. Most statins pass through the liver, and a rise in liver enzymes may suggest the need to lower the dosage or discontinue use of the medication.

Statin-induced rhabdomyolysis occurred in 0.1%–0.5% of patients treated with statins during randomized clinical trials (Graham et al., 2004). Byproducts of muscle tissue are excreted in the urine and can lead to renal failure. Rhabdomyolysis usually occurs with concomitant use of such drugs as erythromycin and azithromycin (Wittert, 2004b). Combination therapy of statins and fibrates increases patient risk for rhabdomyolysis, especially in elderly patients and patients with diabetes (Graham et al.). Table 2 lists other major side effects of these lipid-lowering agents.

Individuals who take statins for long periods of time are most at risk for complications.

Nicotinic Acid

Niacin (vitamin B3) has been shown to decrease triglyceride levels while increasing HDLs by blocking its hepatic uptake and catabolism (Wittert, 2004b). Side effects include flushing, which decreases with duration of use and is often treated with unbuffered aspirin. Niacin initially decreases free fatty acids, but after its effect subsides, the level of free fatty acids rises and impairs the ability of glucose to stimulate uptake and suppress glucose production. As a result, blood sugar levels can rise transiently (Miller, 2003). If niacin is taken at bedtime with food, the likelihood of gastrointestinal disturbances is reduced. Extended-release niacin can be easier to tolerate and is available by prescription. Advicor is a combination of extended-release niacin and lovastatin; it is available with incrementally increasing doses of niacin (Bryan, 2004).

Fibrates

Fibrate therapy benefits those with high triglyceride and low HDL levels and is the first line of defense for patients with these abnormalities (Moon & Kashyap, 2004; Toth, 2004). Commonly used fibrates include gemfibrozil and fenofibrate (Table 2).

Fibrates stimulate hepatic apolipoprotein A-1 expression and lipoprotein lipase activity. If LDL levels increase with use of fibrates, adding a statin may be beneficial. No

Table 2. Lipid-Lowering Medications

Drugs and Dosage	Major Side Effects	Contraindications
<p>Statins</p> <p>Atorvastatin (Lipitor) 10–20 mg/d; maximum 80 mg/d</p> <p>Fluvastatin (Lescol) 20–40 mg/d; maximum 80 mg/d (Lescol XL)</p> <p>Lovastatin (Mevacor) 10–20 mg/d; increase at 4-week intervals to maximum 80 mg/d; with fibrates, niacin, or creatinine clearance <30 ml/min, maximum 20 mg/d</p> <p>Pravastatin (Pravachol) Initially 40 mg/d; may increase to 80 mg/d maximum after 4 weeks; with renal or hepatic insufficiency, 10 mg/d</p> <p>Rosuvastatin (Crestor) 5–10 mg/d; maximum 40 mg/d</p> <p>Simvastatin (Zocor) 20–40 mg/d</p>	<p>Elevated liver enzymes, hepatic injury, myopathy (more likely in patients who are small, frail, or elderly), rhabdomyolysis with renal dysfunction, gastrointestinal (GI) disturbances, headache</p>	<p>Absolute: active or chronic liver disease, pregnancy or nursing</p> <p>Relative: treatment with cyclosporine or macrolide antibiotics, various fungal agents, or cytochrome P-450 inhibitors</p>
<p>Nicotinic acid</p> <p>Niacin (Niaspan) Initially 500 mg/weeks 1–4; 1 g/d weeks 5–8; Increase by 500 mg every 4 weeks to maximum of 2 g/d</p>	<p>Flushing, hepatotoxicity (increased with sustained-release formula), hyperglycemia, hyperuricemia or gout, upper GI distress</p>	<p>Absolute: chronic liver disease, severe gout, pregnancy or nursing</p> <p>Relative: hyperuricemia, uncontrolled type-II diabetes</p>
<p>Fibrates</p> <p>Gemfibrozil (Lopid) 600 mg/d</p> <p>Fenofibrate (Tricor) 54–60 mg/d</p>	<p>Cholesterol, gallstones, dyspepsia, myopathies, upper GI complaints</p>	<p>Severe hepatic or renal insufficiency, pregnancy or nursing</p>
<p>Resins or bile-acid sequestrants</p> <p>Cholestyramine (Questran) 1 packet (4 g) mixed with food or fluid 1–2 times/day; maintenance of 2–4 packets in 2 doses with maximum of 6 packets/d; increase at 4-week intervals</p> <p>Colestipol (Colestid) 5–30 g/d once or divided doses with liquid</p> <p>Colesevelan (Welchol) 625 mg tablets; 3 tablets twice a day or 6 tablets/d in combination with statin 4–6 tablets daily in single or divided doses</p>	<p>Upper and lower GI disturbances (constipation, bloating, dyspepsia), decreased absorption of other drugs, vitamin deficiencies</p>	<p>Absolute: familial dyslipoproteinemia with triglycerides >400 mg/dl</p> <p>Relative: triglycerides >200 mg/dl</p> <p>Precaution: pregnancy or nursing</p>
<p>Cholesterol-absorption inhibitor</p> <p>Ezetimibe (Zetia) 10 mg/d</p>	<p>Elevated transaminases (>3 times normal), GI disturbances, musculoskeletal symptoms, headache</p>	<p>Hypersensitivity to components of the medication, active liver disease, unexplained persistent increase in serum transaminases, pregnancy or nursing</p>

From "Lipid-Lowering Strategies: Today's Therapies and Co-therapies Can Reduce CHD Risk," by K. McDonald, 2003, *Advance for Nurse Practitioners*, 11(12), pp. 24–29; and "Cholesterol: The Good, the Bad, and the Balanced: Part 2—Treatment," by D. D. Wittert, 2004, *Nursing Spectrum*, 17, pp. 24–26.

clinical trial to date has investigated the combined use of fibrates and statins, although it is an option for high-risk patients. However, combined use requires regular monitoring of liver function and CK due to the increased risk of adverse effects (Wierzbicki et al., 2003; Wittert, 2004b). Fibrates should be taken in the morning and statins at night to minimize peak-dose interactions.

Resins or Bile-Acid Sequestrants

Resins, or bile-acid sequestrants, decrease reabsorption of bile in the intestine, leading to increased secretion in stool. The liver responds by increasing the clearance of LDLs from plasma so new bile acids can be formed. Resins do not have an impact on triglycerides but can lower LDL levels with a possible effect of increasing HDLs (Wittert, 2004b). The best-tolerated resin is colestevlam, because it works in the gut rather than systemically (Wittert, 2004b).

Cholesterol-Absorption Inhibitors

The newest class of cholesterol-lowering agents is cholesterol-absorption inhibitors, which are used primarily as an add-on medication to statins (Wittert, 2004b). Ezetimibe (Zetia) was released in 2002; it was demonstrated to affect LDL, triglyceride, and HDL levels alone or in combination with a statin (McDonald, 2003). Ezetimibe enhances the beneficial pleiotropic effects of statins and is also available in a combination drug (Futterman & Lemberg, 2004).

Two pharmacological companies, Merck and Schering-Plough, have combined simvastatin and ezetimibe to produce Vytorin as a combination drug. Vytorin is less expensive and more convenient to take than the two component drugs taken separately. Vytorin has been approved by the U.S. Food and Drug Administration.

Nursing Implications

Neuroscience nurses, in collaboration with other healthcare professionals targeting secondary stroke prevention, need to take an active role in the management of modifiable risk factors, including hyperlipidemia (Mouradian, Majumdar, Senthilselvan, Khan, & Shuaib, 2002). Stroke patients with undesirable lipid panels or a history of CAD need lipid-lowering drugs for prevention of further vascular events (Gomes, Robins, & Babikian, 2002).

Many patients with elevated cholesterol levels also have metabolic syndrome (McDonald, 2003). Patients with high triglyceride and low HDL levels need to be periodically checked for both metabolic syndrome and diabetes mellitus. The ATP III guidelines suggest that practitioners target metabolic syndrome for risk reduction once the primary target of satisfactory LDL levels has been achieved. Treatment strategies for metabolic syndrome include dietary modification, regular exercise, weight, body mass index, and monitoring of drug therapy (Fowler, Moussouttas, & Mancini, 2005).

Identification of risk often begins with laboratory tests. Patient education is critical to obtain accurate blood test results. Nurses need to remind patients to fast for 12 hours before blood is drawn. Patients also need to fast before a blood draw for a hepatic panel, which is often carried out at baseline before statin therapy is started. Additionally, the blood glucose of patients who are taking niacin may be checked periodically, because increases may occur (McDonald, 2003). It is helpful to all involved in a patient's care, including the patient, to create a schedule of necessary laboratory tests.

Lifestyle modifications are an important component of a holistic approach to cholesterol and stroke risk reduction. The ATP III panel (2001) stated that the therapeutic lifestyle changes required to treat lipid disorders are to decrease dietary intake of saturated fat and cholesterol; increase dietary intake of plant stanols and sterols; eat soluble fiber, which may reduce LDL levels; exercise daily to decrease LDL and increase HDL levels; and reduce weight. It has been recommended that dietary intake of saturated fats be reduced to <7% of total calories, that cholesterol intake be reduced to <200mg/day, that intake of plant stanols and sterols be increased to 2 g/day, and that intake of soluble fiber be increased to 10–25 g/day (McDonald, 2003).

Lifestyle modifications are an important component of cholesterol and stroke risk reduction.

Alternative nutritional therapies for achieving optimal blood levels include the use of fish oil or omega-3 fatty acids, which may lower triglycerides. Red yeast rice can lower total cholesterol, decrease LDL, and raise HDL. Policosanol, derived from sugar cane, may raise HDL and lower LDL levels by facilitating hepatic cholesterol synthesis (Wittert, 2004b).

Weight control and physical activity remain important to comprehensive achievement and maintenance of target levels. Collaboration with exercise and rehabilitation therapists and dietitians is important for setting goals and achieving patient outcomes. The American College of Sports Medicine (ACSM, 2005, www.acsm.org) recommends exercising for 30–45 minutes 3–5 days a week, beginning with a warm-up of 5–10 minutes and ending with a gradual decrease in exercise intensity and subsequent cool-down. Burke, Dunbar-Jacob, Sereika, and Ewart (2003) developed an instrument to evaluate self-efficacy in initiating and maintaining recommended diet therapy for cholesterol reduction. Use of this tool advances knowledge of dietary therapy for lipid disorders.

Nurses and pharmacists help patients determine a medication schedule that takes into account proper timing of drugs, side effects, and awareness of drug interactions. For example, statins are usually taken at night to

minimize peak-dose interactions, fibrates are generally taken in the morning, and Advicor is taken once daily at bedtime. Patients need to be educated on adverse effects such as gastrointestinal upset, rash, liver abnormalities, and muscle breakdown (Bryan, 2004). Patients are encouraged to report any changes in bodily function.

A review of all medications is warranted. If statins are taken in combination with niacin or fibrates, the patient may be at increased risk for myopathy. Periodic CK levels and monitoring of muscle strength can help detect increases in adverse effects. Patients should be instructed to avoid eating grapefruit, because it is metabolized in the liver and can increase the adverse effect of statins (Wittert, 2004b).

The treatment plan must be incorporated into the reality of an individual's life (Wittert, 2004b). The patient may resist adjustments in diet or physical activity and may require time to adjust to a new schedule and lifestyle. To monitor progress toward goals, blood cholesterol levels should be checked after the first 6 weeks of treatment.

The future of lipid disorders management may include CETP inhibitors, a vaccine against CETP, and advances in bioengineering of HDLs (Toth, 2004). A new blood test that looks at heart attack risk does not require fasting before blood draw has been developed; it uses the ratio of LDL particles (apolipoprotein-B molecules) to HDL particles (apolipoprotein-A1 molecules) to determine risk. This test may be useful for the prediction of stroke risk in the future.

Summary

Hyperlipidemia is a risk factor for stroke and CAD. Neuroscience nurses play a key role in diagnosis and treatment of hyperlipidemia for patients at risk of stroke by promoting accurate blood sampling, providing appropriate drug prescription and education, monitoring side effects, and supporting lifestyle modifications.

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