Potential Adverse Effects of Statins on Muscle

Many people have high blood cholesterol that may lead to coronary heart disease (CHD). A multifaceted approach consisting of diet, exercise, and pharmacological management is recommended to lower the risk of CHD. Elevated low-density lipoprotein-cholesterol (LDL-C) has been established as a major cause of CHD. The group of cholesterol-lowering drugs known as statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are widely and successfully used in the management of atherosclerotic disease processes that include CHD, myocardial infarction, stroke, and peripheral vascular disease. Statins inhibit the formation of HMG-CoA reductase, which is essential in forming mevalonate, a precursor to cholesterol and other compounds. Lowering LDL-C is the goal of statin therapy, and multiple studies indicate that lowering LDL-C decreases the risk for CHD in people without a history of CHD and decreases the risk for cardiovascular events in people with a history of CHD.

Six statins are currently available, and they are known by a variety of brand names: atorvastatin (Lipitor®), fluvastatin (Lescol†), lovastatin (Mevacor,‡ Altoprev§), pravastatin (Pravachol®), rosuvastatin (Crestor#), and simvastatin (Zocor‡) (Table). Although these drugs have been very successful in managing the cardiovascular health of many patients, there are also potential adverse effects that have been identified. The most common adverse effects reported include muscle pain or weakness that can progress to rhabdomyolysis and mortality. If detected early, statin-related symptoms are reversible after withdrawal of the statin. Early identification of these potentially serious adverse effects can lead to prompt intervention and prevent further complications.


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adverse effects makes the information in this update critical for physical therapists, because they frequently screen patients with musculoskeletal complaints.

Considering that more than 76 million prescriptions for statins were filled in 2000, there was increased concern in the medical and lay communities about the safety of statins. One statin, cerivastatin (Baycol**), was voluntarily withdrawn from the market by the manufacturer in 2001, following its implication in severe adverse muscle reactions and death.

In 2002, the American College of Cardiology, the American Heart Association, and the National Heart, Lung, and Blood Institute (ACC/AHA/NHLBI) issued a clinical advisory about the use of statins. Although the pathophysiology of these adverse effects is not clearly understood, the advisory lists factors associated with an increased risk. The purpose of this article is to describe the adverse effects of statins on muscle so that physical therapists will be better prepared to recognize possible statin-induced myopathy.

### Indications for Statin Use

Guidelines from the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults identified elevated LDL-C as a major cause of CHD and suggested that lowering LDL-C decreases the risk for CHD. Lower LDL-C goals are recommended for patients with multiple risk factors for developing CHD.

The expanding definition of patients who benefit from LDL-C lowering therapy has the potential to expand the overall use of these medications.

More recently, a comparison was made between lowering LDL-C to the recommended level (100 mg/dL with 40 mg of pravastatin daily) versus lowering LDL-C to approximately 70 mg/dL. This more aggressive therapy was achieved by doubling the dose from 40 to 80 mg of atorvastatin in patients with acute coronary events.

Patients who received the more aggressive atorvastatin therapy experienced a 16% reduction in the hazard ratio for death or a major coronary event compared with the moderate therapy group. The most recent findings supporting yet lower LDL-C goals for statin therapy especially for patients at higher risk for developing coronary problems were included in a 2004 update to NCEP's earlier guidelines.

The more aggressive statin therapy protocol being recommended may increase the incidence of adverse events.

Although the incidence of adverse effects is relatively low, millions of people take statins—which could result in cases of myopathy among patients in any given physical therapy practice.

The efficacy of statins to lower LDL-C levels and prevent coronary events is supported in the literature. LaRosa et al. reported the results of a meta-analysis that included 5 randomized controlled trials of 3 of the 6 statins. Approximately 30,000 participants were included and followed for an average of more than 5 years.

Reported findings indicated that statins lowered total cholesterol 18% to 26%, lowered LDL-C 25% to 36%, raised desirable high-density lipoprotein-cholesterol (HDL-C) 5% to 7%, and lowered triglycerides 11% to 17%. The number needed to treat (NNT) was 28 (95% confidence interval = 23–34) to prevent one major coronary event, defined as a coronary death, myocardial infarction, or unstable angina.

The number needed to treat is defined as “the number of patients that need to be treated to prevent one bad outcome.” Use of statins resulted in a reduction in coronary events of approximately 30% regardless of age or sex.

Cholesterol-lowering drugs, therefore, have been shown to reduce the risk of coronary events and coronary death in both the short-term (<10 years) and long-term (>10 years) studies. Clinical trials with large samples are providing more information to substantiate an expansion of application and lower therapeutic goals for LDL-C; therefore, the benefits of statin drugs are becoming more defined.

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* Parke-Davis, Div of Warner-Lambert Co LLC (a Pfizer company), 235 E 42nd St, New York, NY 10017-5755.
* Novartis Pharmaceuticals Corp, One Health Plaza, East Hanover, NJ 07936, and Reliant Pharmaceuticals, 110 Allen Rd, Liberty Corner, NJ 07938.
* Merck & Co Inc, PO Box 4 WPS9–296, West Point, PA 19486-0004.
* Andrx Corp, 411 Hackensack Ave, 3rd Floor, Hackensack, NJ 07601.
* Bristol-Myers Squibb Co, PO Box 4500, Princeton, NJ 08543-4500.
* AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850-5437.
** Voluntarily withdrawn from market by manufacturer (Bayer Pharmaceuticals Corp, 400 Morgan Ln, West Haven, CT 06516).

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All of the statins are associated with the adverse effects of myopathy.\textsuperscript{2,3} \textit{Myopathy} refers to any disease of muscles, acquired or inherited, with symptoms including muscle weakness primarily in the extremities.\textsuperscript{14} Symptoms of myopathy may occur at any time after the initiation of statin therapy.\textsuperscript{2} Factors that may increase the risk of myopathy are age greater than 80 years, being female, small body frame and frailty, multisystem disease, perioperative periods, multiple medications, and concomitant use of certain medications and substances\textsuperscript{2} (Fig. 1). The combination of fibrates or nicotinic acid with statins has been identified as a potential risk factor\textsuperscript{2}; however, recent recommendations support consideration of this combination in patients at high risk for developing coronary events who have elevated triglycerides and low HDL-C.\textsuperscript{11} Warfarin (Coumadin\textsuperscript{14067}), digoxin, and mibebradil (an antihypertensive drug now removed from the market) have been reported to interact with statins in cases of rhabdomyolysis.\textsuperscript{5,15} Hypothyroidism also increases the risk of myopathy in statin users.\textsuperscript{16} Interestingly, patients who may benefit the most from statin therapy also may be the ones with comorbidities and multiple medications that make them at high risk for myopathies.\textsuperscript{17}

The potential for myopathy is dose dependent.\textsuperscript{2,18} This consideration deserves special attention because a higher statin dose with a lower LDL-C target is currently being recommended,\textsuperscript{10} and it is unclear how this will affect the typical initial dosing and thus any adverse symptoms.

### Pathophysiology of Adverse Muscle Effects

The underlying cause of statin-associated myopathy is unclear,\textsuperscript{2,5,10} but there are several theories proposed about the pathophysiological mechanism of injury to skeletal muscles. Statins, or HMG-CoA reductase inhibitors, work by inhibiting the formation of HMG-CoA reductase, which is essential in the production of mevalonate. Mevalonate is a component in the biosynthetic pathway that is shared by cholesterol, ubiquinone, also known as coenzyme \(Q_{10}\) (CoQ\textsubscript{10}), and isoprenylated regulatory proteins.\textsuperscript{5} Thus, statins work effectively, but not selectively, in interrupting the synthesis of cholesterol (Fig. 2).

One theory explaining the adverse effects on muscle involves the interruption in the synthesis of ubiquinone or CoQ\textsubscript{10}. Because statins inhibit the production of mevalonate, a precursor of CoQ\textsubscript{10}, the synthesis of CoQ\textsubscript{10} also may be inhibited. In a cohort of 34 subjects who took a short-term course of atorvastatin, there were decreases in CoQ\textsubscript{10} levels.\textsuperscript{20} Because CoQ\textsubscript{10} is involved in energy production via the mitochondrial respiratory chain, a decrease in CoQ\textsubscript{10} could explain some adverse muscle effects.

This same biosynthetic pathway (mevalonate production) leads to the prenylation, or activation, of regulatory proteins such as guanosine triphosphate (GTP)-binding proteins.\textsuperscript{5} These GTP-binding proteins are important in cell health and control of apoptosis, or cell death. If statins inhibit the activation of these regulatory proteins, uncontrolled cell death may occur. Thus, inhibition of isoprenylated regulatory proteins also may account for adverse muscle effects. Another theory suggests that the reduction of cholesterol in skeletal muscle makes the cell membrane unstable.\textsuperscript{5} Each of these theories continues to be investigated.

### Associated Disease Processes and Symptoms

The clinical presentation of statin-associated myopathies includes lower-extremity pain and weakness associated with stair climbing; inability to open jars; proximal weakness of the shoulder, hip, and knee musculature; and severe muscle cramps.\textsuperscript{6,7} The biceps brachii and masseter muscles, as well as abdominal and low back musculature, also have been reported as being affected, but with less prevalence.\textsuperscript{19}

Associated muscle diseases and symptoms include myopathy, myalgia, myositis, and rhabdomyolysis.\textsuperscript{2,5} The use of the term “myopathy” varies in the literature, and it can occur with or without elevated serum levels of creatine kinase (CK). The CK serum levels are measured to indicate any muscle damage in the system because they are a “biochemical marker of muscle damage.”\textsuperscript{17(p504)}

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Myalgia is muscle pain, aching, weakness, or stiffness without elevated CK levels. Myositis refers to these muscle symptoms with increased CK levels. Rhabdomyolysis is serious muscle damage with CK levels more than 10 times the upper limit of normal. Rhabdomyolysis results in the release of myoglobin into the blood stream, causing possible damage to the kidneys and other organs. Symptoms of rhabdomyolysis include generalized or specific myalgia, muscle tenderness, fever, nausea, vomiting, and dark urine. Its sequelae may include compartment syndrome in the affected muscle group, arrhythmias, acute renal failure, and cardiac arrest.

There is some evidence to indicate that statin use can exacerbate the normal CK elevations seen after exercise. In a randomized controlled trial, Thompson et al examined CK levels after exercise in 59 men with elevated LDL-C who were assigned to either receive 40 mg of lovastatin or a placebo. Exercise consisted of treadmill walking at a 15% downhill grade for a total of 45 minutes and biceps muscle exercise at 50% of the one-repetition maximum weight for 4 sets of 10 repetitions. The CK levels of the group that received lovastatin rose more rapidly in the first 24 to 48 hours after the biceps muscle exercise and were consistently higher at 24 and 48 hours after the treadmill walking (62% and 77%, respectively) compared with the control group. There also are reports of professional athletes who had difficulty tolerating statins because of exacerbated exercise-induced muscle pain. These reports may be of particular interest to patients who are receiving physical therapy, because increased activity and exercise are...
usually part of the plan of care. The long-term effects of exercise and statin use have not been examined. Muscle-related pathologies are most often confirmed by serum CK levels; however, muscle pain or weakness also has been reported without CK elevations. The absence of CK elevation in these instances suggests that the CK level may not be an adequate test for muscle pathology.6,7 Several case studies have used muscle biopsies and electromyography to confirm muscle pathology when CK levels were not elevated. In a case series of 4 patients, Phillips et al6 examined isometric muscle force of hip extensors and hip abductors and muscle biopsy results in patients who were being treated as part of a blinded study of statin therapy. Patients reported pain and demonstrated hip muscle weakness but had normal CK levels when taking the statin. Symptoms resolved during placebo therapy and returned upon blinded re-exposure to the statin, strongly implicating a causal relationship. Biopsy findings suggested that muscle had a mitochondrial respiratory chain dysfunction, as evidenced by increased lipid stores, cytochrome oxidase–negative myofibers, and ragged red fibers. These findings resolved several months after discontinuing the statin.6

For patients being managed solely with statin drugs, the incidence of myopathy is reported as 0.1% to 0.2%.24,28 However, the incidence increases to 1% to 7% for patients taking multiple medications and for those with multiple risk factors for developing adverse events.5,17 Gaist et al29 conducted a retrospective population-based cohort study that examined the risk of myopathy in people using cholesterol-lowering drugs. The 3 cohorts included patients with hyperlipidemia who were using cholesterol-lowering drugs (n=17,219), patients with hyperlipidemia who were not using cholesterol-lowering drugs (n=28,974), and people in the general population who did not have hyperlipidemia and were not using cholesterol-lowering drugs (n=50,000).29 Gaist et al29 reported that the relative risk of myopathy among patients using statins was 7.6 (95% confidence interval=1.4–41.3), suggesting that a person using statins is 7.6 times more likely to develop myopathy than a person not using statins.

Furthermore, Thompson et al5 indicated that less serious side effects of muscle pain and weakness, as opposed to rhabdomyolysis, are underreported and may be 1% to 5%. It has even been suggested that as many as 25% of statin users who participate in vigorous physical exercise could experience muscle aches and cramping that potentially could be dismissed by the patient and the physician.19 If a conservative 5% rate is calculated for the 76 million people taking statins, there could be 3.8 million people experiencing muscle pain or weakness due to the medication.

Safety
There are several recommendations to enhance the safety of these widely used and beneficial drugs. The commonly reported mechanism for confirming adverse muscular events.

Incidence of Adverse Effects
The incidence of statin-associated myopathy is difficult to identify. Clinical trials on drug safety and efficacy report a low incidence of muscle problems. This is demonstrated by a meta-analysis including approximately 30,000 participants in which there were 90 reports of asymptomatic increased CK, 40 in the control group and 50 in the experimental group.12 There were no reports of any clinical muscle symptoms. However, clinical trials often impose strict inclusion criteria and use the lowest, most appropriate dose to attain the target LDL-C level with frequent monitoring.5,17

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![Figure 2.](image_url)
ACC/AHA/NHLBI guidelines recommend baseline measurements of CK in order to evaluate muscle complaints. Prior to the 2004 study in which a lower LDL-C target was recommended, most experts recommended initiating intervention with the lowest possible statin dose necessary to achieve the desired cholesterol goal.

Although some experts have advocated discontinuing statin therapy with symptomatic CK elevation greater than 10 times the upper limit of normal, others have recommended more conservative management by discontinuing statins with a lesser CK elevation or an asymptomatic CK elevation. Medical management may include prescription of an alternate statin or reintroduction of the same statin at a lower dose. The ACC/AHA/NHLBI and other experts have recommended that patients discontinue statin therapy during episodes of acute illness or hospitalization for major surgery because this poses an increased risk for myopathy.

Underutilization of cholesterol-lowering drugs and lack of adherence to the NCEP guidelines have been reported. Recent emphasis has been placed on education to improve adherence to the NCEP guidelines, which advocate cholesterol-lowering measures, including medications. The increased adherence to the NCEP guidelines and the recent findings of decreased mortality and major cardiovascular events with increased statin doses may increase the number of patients taking statins. Physical therapists may encounter even more patients taking statins in their practices.

**Clinical Implications**

Although a recent meta-analysis with approximately 30,000 subjects has shown a low incidence of statin-induced adverse effects on muscle, the number of case reports and published letters suggest that these adverse events may merit additional study. These case reports and letters are indications that many complaints of muscle pain and fatigue or low-grade myopathy often go undetected in the general clinical population. 

Statin-induced myopathy should be suspected if a patient complains of generalized muscle symptoms that are otherwise unexplained and the patient is currently taking a statin. Risk factors and the dose prescribed need to be identified. Myopathy should be considered in elderly patients who demonstrate or describe only muscle weakness because they are less likely to report muscle pain.

A recent example of an adverse muscular event in our practice was seen in an 81-year-old female patient who was frail and was receiving physical therapy in her home after hospitalization for a hip fracture. Her functional abilities suddenly declined so that she could walk only with flexed hips and knees for less than 3 m (10 ft) and was unable to climb steps. She was taking a relatively high dose of atorvastatin (40 mg) and had all of the risk factors identified by the ACC/AHA/NHLBI in Figure 1 except the concomitant use of any of the substances listed. Her family contacted the physician, who discontinued the atorvastatin, and her symptoms subsided within 2 weeks. In contrast, a 74-year-old active man who had been taking a relatively low dose of simvastatin (10 mg) for 5 years and had 3 of the risk factors (multiple medications, multisystem disease, and concomitant use of verapamil) developed proximal lower-extremity muscle weakness. The weakness progressed so that he needed to use his upper extremities to assist his lower extremities into and out of the car. Upon recommendation of the physical therapist, he contacted his physician, who discontinued the simvastatin, and his symptoms resolved within 4 weeks.

There are areas that may be of great interest to physical therapists that have not yet been reported in the literature. Research questions may include: Can physical therapists provide interventions that facilitate the spontaneous recovery that occurs after discontinuation of the statin? Is exercise contraindicated in people who have statin-induced myopathy? Does high-intensity exercise exacerbate complaints of muscle weakness or pain in patients taking statins? These areas of research may become more important as more patients are prescribed these drugs. Until additional evidence indicates otherwise, we recommend that patients with unexplained muscle pain or weakness who are taking statins should be referred to the appropriate physician and that intense exercise should be avoided until the cause of the muscle symptoms is determined.

**Summary**

Statins are widely used drugs to lower LDL-C and reduce risk of CHD. Statins are associated with the adverse effect of myopathy. Although the incidence of adverse effects is relatively low, the fact that millions of people take statins means cases of myopathy could be seen in any given practice. Physical therapists must be aware of this potential side effect, and the risk factors involved, for the overall safety and quality of life of these patients. Appropriate identification of these muscle symptoms in a patient on statin therapy and consultation with a physi-
ciian may ultimately allow the symptoms to reverse. A heightened awareness of the potential for statin-associated myopathy coupled with improved patient education about the signs and symptoms of myopathy is recommended to improve the safe use of these beneficial drugs.

References