Statins have been touted as safe agents that reduce the risk of cardiovascular events, dementia and osteoporosis. However, one statin was recently withdrawn from the market because of concern over rhabdomyolysis. This article reviews the efficacy and adverse effects of statins and presents options for statin-intolerant patients.

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**Q:** What is the efficacy of statins?

Figure 1 depicts the efficacy of statins in five clinical trials. Three concepts arise:

1. Statins given to groups of people always do more good than harm; in each trial the statin-treated group had fewer cardiovascular events (myocardial infarction [MI], new onset angina, sudden death, coronary revascularization) than the placebo-treated groups.
2. The lower the low-density lipoprotein cholesterol (LDL-C), the lower the risk of a cardiovascular event.
3. Patients who have suffered a cardiovascular event (the so-called secondary prevention group) have a much greater risk of cardiovascular events at any given level of LDL-C. In fact, in these clinical trials, the statins reduced cardiovascular risk by about one-third; the higher the baseline risk, the greater the absolute benefit of the statin.

**Lorne’s case**

Lorne, 59, presents having been recently discharged from a cardiology ward. He was originally admitted with ST-elevation myocardial infarction. He received primary percutaneous angioplasty and stenting.

His discharge medications include:
- acetylsalicylic acid, 81 mg daily;
- clopidogrel, 75 mg daily;
- metoprolol, 50 mg twice daily;
- ramipril, 10 mg daily; and
- simvastatin, 40 mg qhs.

He feels generally well and has no symptoms of heart failure, angina or peripheral vascular disease. He stopped smoking while in hospital.

His main concern now is diffuse muscle aching, which waxes and wanes. He learns, via the Internet, that “statins” have been associated with serious muscle problems. He feels he should stop simvastatin.

*How would you advise him? For the answer, go to page 30.*
Table 1 shows the adverse effects of statins, as recently reviewed by Ballantyne and colleagues.2

As with virtually all drugs in the Compendium of Pharmaceuticals and Specialties, statins are associated with nonspecific side-effects like nausea and headache. These are not dose-related and occur with similar frequency in placebo-treated patients.

In my opinion, these side-effects are not usually due to the drugs. Increased alanine transaminase and aspartate transaminase levels occur in a proportion of users and are more common with increasing dose. Interestingly, some patients with pre-existing elevated “liver enzymes” due to nonalcoholic fatty liver disease, may actually improve with statin therapy.

Myopathy, defined as muscle pain and weakness with elevated creatine kinase (CK) levels, is an uncommon side-effect. The more serious muscle problem, rhabdomyolysis, has been reported in only 601 patients worldwide as of October 2004.

All authorities recommend measuring CK if muscle pain and weakness occur. If the CK is 10 times normal, the statin should be stopped. Remember that this adverse effect occurs more commonly at high doses and is more common in females, the elderly, patients with hypothyroidism and in patients taking other drugs, particularly gemfibrozil and cytochrome P450 3A4 inhibitors.

One recent study showed adding verapamil, 120 mg daily, to normal volunteers taking simvastatin, 40 mg daily, caused a fourfold increase in simvastatin blood levels. These adverse effect statistics were gleaned from clinical trials and reports to the U.S. Food and Drug Administration.

Franc surveyed 815 patients attending a lipid clinic and taking statins. Almost 20% complained of muscle pain, cramps or stiffness, which they attributed to the statin. Few had a greatly elevated CK.4

Moreover, Phillips and colleagues reported on four patients with a history of muscle symptoms while on a statin, who were given a statin or placebo in double-blind, crossover fashion for nine weeks.5 All identified the statin period, but none had an elevated CK. Muscle biopsies were abnormal in all four and returned to normal a few months later.

This study raises the possibility of statins causing symptoms and pathologic abnormalities without a CK rise. However, musculoskeletal complaints are common within the general population.

About the author...

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Also, we have no information on the eventual outcome of patients with symptoms, but no CK rise. Statins have also been linked with memory loss, but causality is tenuous at best.

**Q:** Should I prescribe another statin?

There is surprisingly little literature on whether patients intolerant to one statin will do better on another. One 43-year-old man with hypothyroidism (a known risk factor) developed rhabdomyolysis while taking atorvastatin. After correction of the risk factor, simvastatin was started and increased to a dose of 80 mg daily. The patient remained well for at least a year.6

In my own experience, substituting another statin is worth a try.

**Q:** Should I add coenzyme Q10?

An early report in 1990 described four patients with heart failure whose myocardial coenzyme Q10 concentration fell after lovastatin was added.7 All developed worsening heart failure that improved with coenzyme Q10, 100 mg to 200 mg daily.

A more recent report appears to confirm diastolic dysfunction can occur after statins and can be reversed by coenzyme Q10.8

I have recommended coenzyme Q10 to some patients taking statins who have muscle pain, but normal CK; it works occasionally.

**Q:** Should I recommend only diet and exercise?

In patients with hypercholesterolemia, diet alone reduces LDL-C by 10%, at most. On the other hand, reducing cholesterol is not our main goal, rather it is preventing cardiovascular disease.

Chahoud recently reviewed 10 long-term diet studies.9 He found diets reduced cardiovascular events by 29% to 64% in one to eight years. Common to all diets studied were decreased trans fatty acids and reduced calories.

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The “Mediterranean” diet, which is fairly low in carbohydrates, but rich in omega-3 fatty acids, reduced the mortality rate to 4.6% in 46 months, compared with the “control” diet rate of 7.9%. This 56% reduction in mortality is impressive, but needs confirmation.

It seems sensible to recommend a calorie-reduced, low-saturated-fat diet to all post-MI patients. Few experts would rely on diet alone.

**Q: Should I recommend another lipid-lowering medication?**

In patients with diabetes and coronary artery disease, fenofibrate reduces both atherosclerosis progression and cardiovascular events. Another drug, ezetimibe, can lower LDL-C by up to 20%.

Unfortunately, we have no long-term outcome studies in post-MI patients with either drug.

More on Lorne

Creatinine kinase (CK) should be measured. If it is 10 times the upper limit of normal, the statin should be stopped.

Lorne should be screened for hypothyroidism and questioned about other drugs. Even if these risk factors are present, I would hesitate to prescribe another statin.

If the CK is five to 10 times normal, it should be repeated in a few days. If it is increasing, the statin should be stopped. If the CK is normal or only slightly elevated and there is no muscle weakness, Lorne should be informed of the benefit of continuing the statin.

A trial of a different statin is worthwhile. If three or more statins cause side-effects, a trial of coenzyme Q10, 100 mg to 200 mg daily, might be considered.

Also, consider a trial of ezetimibe, with or without fenofibrate, particularly if the high-density lipoprotein cholesterol is low.

By all means, Lorne should be referred to a dietitian and instructed on a heart-healthy diet. He would also benefit from a cardiac rehabilitation program.

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† One price for all dosage strengths. Price does not include pharmacy professional fees. Please refer to Product Monograph for complete dosing information.
References

The most frequent adverse events for ACCURETIC* in controlled trials were headache (6.7%), dizziness (4.8%), cough (3.2%) and fatigue (2.9%). For the complete list of adverse events, please refer to the Product Monograph.