Benefit vs Risk of Statins

Number 92 September 2004

In many *Heartbeats* we have urged you to treat more people with higher doses of statins, most recently with the summary of the updated NCEP/ATP III Guidelines in August's issue. Because statins are prescribed so frequently, for long periods of time, and are most commonly used in middle-aged or elderly patients, who tend to be taking many other medications, safety concerns are heightened.

This *Heartbeat* will address the complexity of the downside risk of statins, even as we urge you to treat more people to more aggressive goals even in the elderly, who are at higher risk of adverse events. The potential benefits of statins far outweigh their risk. But it is important to know when to "bail." We'll cover who is at more risk and how to identify that risk so it can be decreased, while still maximizing potential benefits of lipid-lowering treatment.

Benefits

As a class, the statins are remarkably safe, and their use in patients who need LDL lowering for athero-prevention has a very high benefit/risk ratio. There is compelling evidence from five recent outcomes trials with 50,000 patients showing benefit that resulted in the modifications to the NCEP ATP III Guidelines in July of this year.[1] There were no changes in the low risk and low moderate risk groups. More aggressive recommendations were made for the very high high-risk group (LDL-C < 70 mg/dL) and high moderate risk groups (LDL-C < 100 mg/dL)—Table 1. These new recommendations are anticipated to expand the number of Americans who should be taking statins from 36 million (although only 11 million actually do) to as many as 50 million.

Data from the Collaborative Atorvastatin Diabetes Study (CARDS)[2], showing a 37% reduction of cardiac events with atorvastatin 10mg compared to placebo in 2838 T2DM patients with relatively low LDL-Cs, further support the Health Protection Study (HPS) findings[3]. The conclusion was, that the data is strong enough to state that strong consideration

Table 1. New Modifications To NCEP ATP III.

Risk category	LDL cholesterol goal
High Risk: CHD, PAD, carotid vasc dx, AAA or CHD risk equivalents (DM or 10-year risk >20%).	<100 mg/dL
Very High Risk: above plus have multiple risk factors including diabetes, tobacco dependence, metabolic syndrome, or severe or poorly controlled risk factors (eg HBP) or recent MI, acute coronary syndrome or recurrent problems on treatment.	**New:** optional goal of <70 mg/dL
Moderate Risk: two or more risk factors (10-year risk <10%).	<130 mg/dL
High moderate Risk: two or more risk factors (10-yr risk 10—20%)--ex. MetS	**New:** optional goal of <100mg/dL.

be given, to adding a statin to anyone with T2DM, regardless of LDL-C level. They should be at least 40 years of age and have at least one other high-risk feature, including hypertension, retinopathy, albuminuria, or current smoking. This data will further expand statin usage.

The "Z" phase of the Aggrastat to Zorcor (A to Z) study, which compared early intensive (40mg of simvastatin for a month followed by an 80mg dose) to a conservative regimen (20mg of simvastatin after 4 months of placebo) in 4497 acute coronary syndrome patients resulted in a favorable trend toward reduction of major CV events.[4] These results weren't nearly as strong as PROVE-IT[5], and the high

dose regimen had significant safety concerns [9 developed myopathy (10x normal CPK), and 3 of those had CPK levels > 10,000 units/L and met the definition of rhabdomyolysis].

Risks

Medication safety is always an issue, but because of the ever increasing numbers of patients who should be taking statins, older age and the polypharmacy typical of those who require statins, and the higher doses recommended, safety concerns are heightened and of great interest to the public.

Muscle Problems: There are four interrelated terms for muscle problems that can occur and are often confused (Table 2).

Table 2. Definitions

Muscle Problem	Definition
Myopathy	General term for disease of muscles usually characterized by weakness. In the setting of statin Tx, used to describe any muscle problem regardless of whether it is related or not. True definition should be myalgia plus a CPK > 10x normal.
Myalgia	Refers specifically to pain in the muscles, which is often seen with statin based myopathy.
Myositis	Term reserved for inflammation of the muscles confirmed by biopsy. Not very practical.
Rhabdomyolysis	Extreme form of myopathy in which inflammation breaks down muscle in large quantities (CPK > 10,000) resulting in large amounts of myoglobin that overwhelms the kidneys.

It is important to note that myopathy is more common than we think (far greater than the < 1% reported) and is not always associated with pain or an elevated CPK.[6] Painless myopathy is common, presenting only with weakness or stiffness. Patients have to be instructed to report ***pain*** **and/or** ***weakness and/or stiffness.*** Due to its seriousness, rhabdomyolysis is much better prevented than treated, so we must do our best to see that myopathy doesn't progress to rhabdomyolysis.

CPK should be measured baseline and then only with symptoms. Even though the degree of CPK elevation can be useful in estimating severity or assisting in diagnosis when symptoms are equivocal, if the patient has convincing myopathic symptoms and a normal CPK, the patient should be treated as having true myopathy. Correlation between myopathy and CPK is not great, and even severe myopathy can have normal or minimally elevated CPK. However, if CPK is > 10x normal at baseline or while on therapy, statins shouldn't be initiated or stopped.

Risk factors for myopathy are: female gender, advanced age (> 60), dehydration, underlying renal or liver disease, and concomitant medications—a fairly long list but specifically combination lipid-lowering therapy with a fibrate. Statin-induced myopathy is strongly dose related, so low doses of a given statin are usually less likely to cause myopathy than higher doses. For this reason, and perhaps because muscle benefits from statin-free periods of recovery, every-other-day dosing of a statin can be helpful in reducing muscle symptoms.

There are differences among the statins in terms of their propensity to cause myopathy. Their risk is not directly proportional to cholesterol-lowering efficacy (relatively low with atorvastatin compared to zimvastatin); however, the two statins that appear to have lower-than-average risk of myopathy, fluvastatin (*Lescol*, Reliant) and pravastatin (*Pravachol*, Bristol-Myers Squibb), are the least potent statins. These can be especially useful in patients with symptoms or risk of myopathy. Scientific evidence is stronger for fluvastatin having the lowest myopathy risk, even though historically pravastatin (less water soluble and not metabolized through the CY P450 system) has been considered by many as the only safe statin. In the Assessment of Lescol in Renal Transplantation (ALERT) trial 1000 patients took fluvastatin in combination with cyclosporine and had no increase of myopathy compared to another 1000 patients on placebo.[7] This is impressive evidence for a low myopathy risk with fluvastatin (possibly secondary to its extended release formulation associated with reduced tendency of systemic complications or its metabolism through the

cytochrome P450 2C9 pathway making it less prone to drug interactions).

The Negative placebo effect of statin therapy is common and necessary unfortunately. We are required to create an adverse expectation when initiating statin therapy. Most patients are already concerned about safety issues because of information either from TV or the pharmacist, and we are obligated to point out its possible adverse symptoms and effects to liver and muscle. *This should be balanced by telling them that the beneficial outcomes benefits far outweigh the risks.* The patients' heightened awareness is good in that, if something negative happens, they are more likely to notice it early and contact us. But it also means that we're setting the patient up to find problems that don't truly exist—everyone has aches and pains. The good news is that we can turn this to our advantage if a patient reports symptoms of myopathy. We can explain that the myopathy often resolves with whatever course of action we have chosen—having the patient continue, temporarily stop, reduce the dose, change drugs (anecdotal evidence suggests that switching often resolves symptoms), or stop statins altogether—suggesting that his/her symptoms will improve soon. We thus create a *positive placebo situation*, increasing the likelihood that symptoms *will* resolve. Obviously we can't ignore a true myopathy, but it's reasonable to try to reverse their negative anticipation, which may worsen any symptoms present.

Liver Problems: The classic definition of hepatotoxicity is an increase in serum transaminases of at least 3 times the upper limit of normal or more, and that ranges with statins from a low rate at lower doses of about 1 in 1000 (0.1%) up to about 2.5%. Most patients who get increases in LFTs have no symptoms of liver disease. In most cases the patient is simply asymptomatic with a biochemical abnormality, which allows you to repeat the test. If it persists, you might need to consider altering therapy. But in many cases that repeat test is normal, and you don't really need to do anything at all.

If the elevation is more significant, you can stop the drug and then consider rechallenging the patient at the same dose. If it is more severe, you can lower the dose of the same statin, since transaminase elevations are usually dose-related. Finally, you can switch to a different statin. Of course, you can always try to reduce or eliminate the adverse effects of other hepatically adverse factors, such as other hepatotoxic drugs. There does not appear to be any large difference among statins in terms of risk of transaminase elevations. Risk factors for transaminase elevation are advanced age, female gender, alcohol use, and prior history of hepatitis. Individuals with chronic active hepatitis are not good candidates for statin therapy. But one subset of patients with hepatitis [those with nonalcoholic steatohepatitis (NASH), in which the hepatitis is due to fatty infiltration of the liver] may actually improve with a statin or other lipid-lowering agent.

Transaminase measurements should be done at baseline. If one reading is > 3x the upper limit of normal, a statin should not be started except to treat NASH. Follow-up usually consists of another transaminase at the next visit, usually after 2 or 3 months. If a transaminase elevation occurs, it usually happens early in the course of the statin use, so a single measurement after starting the statin is usually sufficient. The one exception to this rule is a patient with underlying liver disease or at high risk of it, such as a binge drinker. In lower-risk patients, transaminases need be measured in follow-up only if the statin dose is increased, if the patient is switched to another statin, or if another medication like niacin, a fibrate, or ezetimibe is added.

Combination Lipid-lowering Therapy

The rational of combination therapy is that, almost without exception, adding another lipid-lowering agent to a statin will give at least an additive benefit, and in most cases an additional benefit that a statin cannot give. As we learn more about athero-prevention and the benefits of other targets for therapy (HDL-C, Triglycerides (TG), etc.) and more aggressive goals of these targets, combination therapy will become more appealing. It will be beneficial not only in terms of efficacy with regard to lipids and athero-prevention, but also from a safety standpoint. Not every patient who needs to be treated for dyslipidemia should get 2 or more drugs, but in general we are under-treating our patients. Combination therapy is often a much better way to increase treatment benefit than uptitration of statin monotherapy and seems to be the *wave of the future*.

As the continuing benefits of LDL-C lowering with statins unfolds, new data suggests that even a lower level of LDL-C is better in patients identified as

being higher risk. Even with more effective statins, cost, safety, and logistical concerns often make it impossible to attain these new desired levels of LDL-C with statin monotherapy. The problem is that doubling the dose of any statin gives only about an additional 6% LDL-C lowering effect, while that same doubling may bring a significant increase in cost, and a geometric rise in potential toxicity.

Benefits of statin combination treatment are independent in terms of athero-prevention. For example, niacin lowers lipoprotein (a) and is much more effective in raising HDL-C, giving an added dimension beyond that of a statin alone. Fibrates are more effective than statins for lowering TG. Ezetimibe (Zetia, Merck), which is not a very potent HDL-C-raising or TG-lowering drug, will add to the HDL-C-raising effect and the TG-lowering effect of statins, just as it helps attain the lower LDL-C levels with lower risk than the high dose statins.

Most statins reduce CV events by 20% to 35%. Studies of combination therapy have generally shown an event reduction of 70% to 90%, and even though we cannot extrapolate directly from this, clinical data strongly suggest that combination therapy is much more efficacious in reducing CV events, not surprising given that the lipid-lowering effect is much greater. Only two combinations are available at this time. Extended release niacin (Niaspan, Kos) and generic lovastatin combined (Advicor, Kos) appears to carry no excess myopathy risk. Added risk of myopathy with niacin plus a statin appears to be at least as low as it is with a fenofibrate (in the extended release forms). As you know, fenofibrate (Tricor), although more expensive, appears to be safe in combination with all statins. This is in contrast to the fibrate (gemfibrozil) which increases statin levels, possibly CPK levels and muscle symptoms when administered with all statins except fluvastatin and not nearly as much with pravastatin. The only other available combination lipid-lowering agent is the recently released Vytorin (simvastatin plus ezetimibe, Merck/Schering Plough), which obtains comparable LDL-C lowering with lower statin doses (less risk) and appears promising. However no outcomes data are available.

Conclusions:

As a class statins are remarkably safe and beneficial and have a very high benefit-to-risk ratio. Because of the new mandate to use higher doses in patients at higher risk of complications and potential for drug interactions, safety issues have to be addressed. Patients have to be informed of potential safety risks, and any symptoms or signs of problems must be taken seriously and handled properly. Safety, cost and efficacy considerations may often lead to use of lower doses of a given statin, use of safer statins (pravastatin or fluvastatin) and use of other agents in combination with a statin for greater LDL-C lowering and/or other lipid benefits, even in the advent of lower LDL-C goals.

Mario L Maiese, DO, FACC, FACOI Associate Professor of Medicine UMDNJSOM
Mail to: maiese1@comcast.net

[1] Grundy SM et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* July 13 2004; 110: 227-239.

[2] Colhoun HM et al. Primary prevention of CVD with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. *Lancet* August 21 2004;364: 685-696.

[3] Heart Protection Study (HPS) Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet.* 2002; 360: 7–22.

[4] De Lemos JA et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes (AtoZ). *JAMA* September 15 2004;292: 1307-1316.

[5] Cannon CP, Braunwald E, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* April 8 2004; 350: 1495–1504.

[6] Phillips PS et al. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med 2002; 137:581-585.

[7] Holdaas H et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomized, placebo-controlled trial. *Lancet* June 3 2003; 361: 2024-2031.