

## Getting More People on Statins

**S**tatins have been available in the United States since 1987, and yet 15 years later most patients who have had atherosclerotic events and/or diabetes mellitus, or who are at high risk for atherosclerotic events are not on statin therapy despite its proven benefit in decreasing first and repeat atherosclerotic events. The following are my recommendations for increasing the numbers of patients on statin therapy.

1. *Shift the emphasis from secondary prevention and diabetes mellitus to primary prevention.* Do not wait to start statin therapy until after an atherosclerotic event has occurred or diabetes mellitus has appeared. By the time either has appeared  $\geq 1$  major epicardial coronary arteries have been narrowed  $>75\%$  in cross-sectional area by atherosclerotic plaque.<sup>1,2</sup> Guidelines for lipid-lowering therapy, formulated by the Adult Treatment Panel of the National Cholesterol Education Committee in 1988, and revised in 1993 and in 2001, are based on *decreasing the risk of developing first and repeated atherosclerotic events.*<sup>3</sup> Because it is rarely genetic in origin (the familial variety is present in only about 1 in 500 people<sup>4</sup>), atherosclerosis in my view needs to be approached not primarily from the standpoint of decreasing risk but from the standpoint of actually preventing and/or arresting plaque formation. Pediatricians do not talk in terms of decreasing the risk of measles, mumps, pertussis, and polio. They focus on total prevention of these conditions. The same approach can be applied to atherosclerosis.

But what serum cholesterol numbers are necessary to prevent atherosclerotic plaques from forming? The evidence is substantial that if over decades serum total cholesterol is  $<150$  mg/dl, the low-density lipoprotein (LDL) cholesterol  $<100$  mg/dl, and the high-density lipoprotein (HDL) cholesterol  $>20$  mg/dl, the chances of forming atherosclerotic plaques are slim. (I realize that many readers will be shocked by the mention of an HDL cholesterol of only  $>20$  mg/dl. But this number is only used when the total cholesterol is  $<150$  mg/dl and the LDL cholesterol is  $<100$  mg/dl.<sup>5</sup> If the total cholesterol is 200 mg/dl and the HDL cholesterol is only 21 mg/dl, an atherosclerotic event is likely.) Because about 45% of adults in the Western World die from cardiovascular disease, these numbers need to be the goals of *all adults*, not just adults with atherosclerotic events and/or diabetes mellitus, and now lipid-lowering agents, which can achieve these goals in most patients, are available. Thus, lower the bar for those eligible for statin therapy!

But how can these therapies be afforded the argument goes? These numbers can be achieved by following a vegetarian-fruit diet, which is the least expensive route. If that route is unsatisfactory simply decreasing the quantity of flesh (muscle) consumed by

one half would free up enough money to purchase the lipid-lowering agent(s). We seem to afford arterial angioplasty and stents, bypass, endarterectomy and resection, and expensive diagnostic tests, and pacemakers and defibrillators without excessive thought, and yet there is no evidence that either arterial angioplasty or bypass prolongs life. In contrast, lipid-lowering therapy prolongs life by decreasing atherosclerotic events including stroke.<sup>6-11</sup> Thus, I say serum LDL cholesterol should be  $<100$  mg/dl, total cholesterol  $<150$  mg/dl, and HDL cholesterol  $>20$  mg/dl for everybody. By doing this, the guidelines would be immediately simplified, and there would be no separation of so-called primary and secondary prevention or distinction between diabetics and nondiabetics.

The average LDL cholesterol in persons in coronary care units with acute coronary syndromes is about 145 mg/dl, and yet according to the most recent guidelines an LDL cholesterol of 159 mg/dl in a patient with only 1 or no other risk factor is considered "borderline" and not worthy of lipid-lowering drug therapy. This recommendation makes little sense to me. The Heart Protection Study<sup>11</sup> demonstrated a significant reduction in first and repeat atherosclerotic events by simvastatin therapy in patients with pretreatment serum LDL cholesterol levels  $\leq 115$  mg/dl. In contrast to lipid-lowering agents, aspirin is recognized to decrease atherosclerotic events irrespective of the platelet count or the "stickiness" of platelets. Likewise, the prophylactic value of lowering an elevated systemic arterial pressure is well recognized irrespective of the magnitude of blood pressure elevation.

2. *Eliminate the need for titration of statin drugs.* This is done by starting the patient initially on the proper dose, i.e., the one that lowers the LDL cholesterol to  $<100$  mg/dl. A major reason patients do not achieve this LDL cholesterol goal is that the statin dose is too low and the dose is never raised. If the initial LDL cholesterol level is 185 mg/dl, for example, a drop of slightly  $>45\%$  will be necessary to achieve an LDL cholesterol of  $<100$  mg/dl. As shown in Table 1 that would require 40 mg of atorvastatin or 80 mg of simvastatin.

In contrast to statins, niacin therapy needs to be titrated, starting with a low dose (such as 500 mg) and gradually increasing to 1,500 mg if necessary. Likewise, fibrates might best be titrated—at least when added to a statin drug.



**TABLE 1** Comparative Efficacy of the Five Currently Available Statin Drugs

Statin Drug (mg)	Serum Cholesterol	
	Total	LDL
Atorvastatin (Lipitor)		
5	22% ↓	27% ↓
10	27% ↓	34% ↓
20	32% ↓	41% ↓
40	37% ↓	48% ↓
80	42% ↓	55% ↓
Simvastatin (Zocor)		
10		
20		
40		
80		
Lovastatin (Mevacor)		
20		
40		
80		
Pravastatin (Pravachol)		
20		
40		
80		
Fluvastatin (Lescol)		
20		
80		

Modified from Roberts WC. The rule of 5 and the rule of 7 in lipid-lowering by statin drugs. *Am J Cardiol* 1997;80:106-107.

3. *Eliminate the requirement for liver function tests.* The concern of hepatic dysfunction by physicians and patients frightens patients, and yet acute liver failure produced by a statin drug is incredibly rare (1/1 million patient-treatment years), a rate approximately equal to the rate of idiopathic acute liver failure.<sup>12</sup> The evidence that liver failure is ever the result of statin therapy is at best tenuous! Minor elevations in hepatic enzymes, i.e., serum alanine aminotransferase enzyme (ALT), occur in 2.6 % and 5.0% of patients on lovastatin 20 and 80 mg/day, respectively.<sup>12</sup> These elevations are reversible with continuing therapy, are dose related, and are probably related to the cholesterol lowering per se!<sup>12</sup> (Elevation of the serum aminotransferase [AST] levels can occur with either muscle or liver injury and is thus less specific than elevation of the ALT level.<sup>13</sup>) In all of the 5-year, double-blind, placebo-controlled statin trials,<sup>6-11</sup> no patient was permitted in the trial if his/her baseline ALT or AST was >3 times the upper limit of normal. When these trials were initiated, it was not appreciated that hepatitis C was common (estimated 3 million patients in the United States) or that fatty liver, a cause of ALT elevation, was present in probably 50% of patients with diabetes mellitus, and there are an estimated 17 million diabetics in the USA. Alcoholism can also alter hepatic enzymes and there are probably 10 to 12 million habitual alcoholics in the United States. In other words, there are several causes for elevation of serum ALT. The danger for a patient with an elevated serum LDL cholesterol is arterial not hepatic! Additionally, there is no evidence that statins further elevate ALT when the level of this enzyme is raised by another condition.<sup>12</sup>

The requirement to do liver function tests in patients on statins needs to be removed from the package insert! If this were done, the money now applied to tests for hepatic dysfunction could be applied to purchasing the drug, and a malpractice worry would be removed from the concern of physicians, and worry about potential liver damage could be removed from the concern of both patients and physicians. There is no logic in requiring liver function tests periodically for patients on statins but not for patients on fibrates or niacin. Television ads that call attention to the potential danger of statins to the liver frightens patients unnecessarily and many patients appear to worry more about their liver than they do their arteries. This worry

may be one reason why about 50% of patients on statins discontinue them in 1 year.

The only major concern of statin therapy is *myopathy* and that occurs in about 1 in 10,000 person-years, a multifold risk less than the consequences of accumulating atherosclerotic plaques in arteries.<sup>12</sup> In contrast, the risk of myopathy for patients on a fibrate is nearly 7/10,000 person-years.<sup>12</sup> For the general population, which is not on either a statin or a fibrate, the risk is 0.2/10,000

patient-years.<sup>12</sup> Elevation (<3 times the upper limit of normal) of the serum creatine phosphokinase (CPK) occurs in as many as 30% of dyslipidemic patients not taking lipid-lowering agents.<sup>13</sup> The risk of myopathy is less than that of a major bleed in patients taking aspirin or a nonsteroidal anti-inflammatory drug.

In summary, atherosclerosis needs to be viewed as a potentially preventable disease. Atherosclerosis needs to be discussed in terms of plaque prevention, not in terms of decreasing risk. This means that LDL cholesterol in all adults needs to be <100 mg/dl with HDL cholesterol as high as possible but at least >20 mg/dl when the total cholesterol is <150 mg/dl. If patients are started on the dose of statin that lowers the LDL cholesterol to <100 mg/dl from the beginning, this action will usually eliminate the need for statin titration. Baseline and periodic liver function tests also need to be eliminated because the evidence that statin therapy alters them is tenuous and the fright produced in patients from worry about their liver may play a role in their discontinuing statin therapy. Monitoring for hepatotoxicity is ineffectual in preventing serious liver disease and it may increase the risk of atherosclerotic events because of needless discontinuation of cholesterol-lowering therapy for false-positive results in patients who are benefiting from statin treatment. And finally, statin drugs not only decrease the frequency of coronary events but also stroke (by 30%).



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