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From the Desk of Dr. Stephen Sinatra

Is Cholesterol Lowering with Statins the Gold Standard for Treating Patients with Cardiovascular Risk and Disease?

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"Treatment of Patients with Lipid Disorders in the Primary Care Setting: New Treatment Guidelines and Their Implications"[1] presents a thorough review of the lowering of lipid levels in patients with and without atherosclerosis. The author endorses the new National Cholesterol Expert Panel, Adult Treatment Panel III treatment recommendations targeting low-density lipoprotein cholesterol (LDL-C) as an entity to be treated aggressively by the use of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins).[2] Although statins can significantly reduce rates of coronary morbidity and mortality, using LDL-C values as the focus to implement therapy may be inappropriate for the following reasons:

1. Adherence would require a threefold increase in the number of Americans being prescribed statins, bringing the total to 36 million people taking HMG-CoA medications. As many as 1 in 6 American adults could potentially be advised to take these drugs, at a cost of approximately $30 billion,[3] placing an enormous financial strain on the proposed governmental program for prescription drug coverage.
2. The oxidation of LDL-C remains a hypothesis,[4] yet cholesterol levels continue to drive treatment interventions.
3. Intriguing research results on ω-3 fatty acids[5,6] demonstrate improved survival rates for subjects with known cardiac disease, supporting the theory that assuaging inflammation confers coronary risk reduction. Decreases in the rates of sudden death, cardiovascular death, and all-cause mortality[6] associated with high levels of ω-3 fatty acid intake were observed to be independent of cholesterol levels.
4. Multiple physiologic markers for inflammation are known to enhance cardiovascular risk, and statins may have preventive and therapeutic interventions through their anti-inflammatory mechanisms.[7]
5. Statin therapy is associated with a reduction in the incidence of recurrent coronary events after myocardial infarction by reducing inflammation, rather than by lowering cholesterol level.[8]
6. Recent investigations suggest that the cardioprotective properties of statins may be more related to their anti-inflammatory effect than their ability to lower lipid levels. Approximately 50% of myocardial infarction patients have a normal LDL-C value, and C-reactive protein (CRP) level may be the best predictive marker for atherosclerotic events.[9]
7. Compared with patients receiving statin medication (for LDL-C levels >125 mg/dl), untreated subjects whose hs-CRP levels were not elevated did not have an increased risk of recurrent cardiac events, while those whose hs-CRP levels were elevated had significant risk of fatal coronary events, regardless of their LDL-C levels.[10]

It is obvious that statin therapy confers protection in terms of cardiovascular disease risk but is this beneficial effect due solely to lowering of cholesterol level? Researchers attempted to answer this question in a recent study of 1,616 patients.[11] Patients hospitalized for an acute coronary event whose statin drug was discontinued were nearly three times as likely to have a nonfatal myocardial infarction or die, compared with their counterparts who continued to receive statin therapy. Investigators proposed that those taking the HMG-CoA drugs appreciated a smoother course because of an entirely different mechanism than reduction of cholesterol level.

In another study involving 1,707 consecutive patients undergoing coronary arteriography, 985 were found to have severe coronary artery disease. More than 100 of these patients died within 3 years, yet lipid measurements failed to predict survival.[12] Although serum CRP levels did correlate with mortality rate, notable prognostic indicators included age, ejection fraction, and severity of diabetes. Initiation of statin therapy was associated with improved survival rate, especially in those patients with the highest CRP levels.

The Heart Protection Study[13] evaluated women, the elderly, diabetics, people with low baseline cholesterol levels, and those with prior occlusive noncoronary vascular disease. Results demonstrated the positive impact of simvastatin therapy across all patient groups, independent of cholesterol levels. Even in subjects with acceptable LDL-C levels (<100 mg/dl), there was a clear reduction in the incidence of major

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cardiovascular events, indicating that risk reduction for cardiovascular disease is not the result of the ability of HMG-CoA to reduce LDL-C level.

The emerging literature clearly suggests that the cardioprotective properties of statins are related more to their anti-inflammatory activity than to their lipid-lowering effect. Perhaps physicians should consider prescribing statins for any high-risk cardiac patient, regardless of cholesterol level, and especially for those patients with systemic markers of inflammation. In this population, the risk-benefit ratio truly justifies treatment.

We cannot fail to consider the side effects of drugs that lower cholesterol levels, however, because properly prescribed pharmaceuticals remain the fourth leading cause of death in the United States.[14] Overreliance on pharmacologic agents remains controversial, and the cerivastatin disaster[15] has been a clear example of how dangerous statins can be to some people. Longitudinal studies looking into the efficacy and risk of long-term statin therapy (>10 yr) are lacking.

For example, Newman and Hulley[16] observed the carcinogenicity of lipid-lowering drugs in rodents and suggest that these medications be avoided except for short-term interventions in those at very high risk for coronary heart disease. Statin studies have been conducted for an average of only 5 years, although a recent follow-up report from the Scandinavian Simvastatin Survival Study (4S)[17] was reassuring with regard to survival benefits and cancer risk after 7 years; however, that time frame may still be insufficient for the expression of cancer to be fully realized.

The Cholesterol and Recurrent Events study[18] reported a higher rate of breast cancer than expected in 576 postmenopausal women. Twelve women taking statins developed breast cancer, compared with only one reported case in the control group; this difference is highly statistically significant.[19] Although the Cholesterol and Recurrent Events study investigators reported this finding as a statistical anomaly, it definitely raises a red flag for concern because it is still more than double the expected rate of five breast cancer cases for this cohort.

It is well known that statins lower serum levels of the antioxidant nutrient, ubiquinone (Q10) (formerly known as coenzyme Q), using the same biochemical pathway by which they disrupt cholesterol synthesis.[19] Lower Q10 levels have been incriminated as one contributor to breast cancer,[20] a finding that should be a cause for discretion when prescribing statins to postmenopausal women, a high-risk population for breast cancer.

Other side effects of statins include polyneuropathy,[21] liver dysfunction,[22] rhabdomyolysis,[23,24] myalgia, and myopathy.[25] There are also data supporting rapid improvement of statin-induced myalgia and fatigue when supplemental Q10 is administered.[26] These observations may be relevant to two patents held by Merck and Co., Inc. (Whitehouse Station, NJ), for combining Q10 with a statin in the same capsule: US Patent 4929437, issued May 29, 1990; and US Patent 4933165, issued June 12, 1990; both are entitled "Coenzyme Q10 with HMG-CoA Reductase Inhibitors."

With millions of Americans who will be taking statins for decades, as recommended by the NCEP guidelines, long-term side effects will become apparent, creating a whole host of pathologic situations. What does all of this confusion and controversy mean to practicing primary care physicians, and, most important of all, to the patients for whom they care? Dietary factors and therapeutic lifestyle changes have no side effects and must be considered as the first line of defense in preventive cardiology.[27]

There is little doubt that statin therapy can significantly reduce the incidence of coronary morbidity and mortality, especially for those who are at greatest risk of developing coronary artery disease,[28] and under use of statins in this population should be strictly avoided. With recent investigations using electron beam computed tomography demonstrating the association between high coronary calcium burden score (>1,000) and cardiac events,[29] statin therapy may prove to be a reasonable intervention, regardless of LDL-C levels. Using LDL-C values as guidelines for treatment is clearly not appropriate.

As research continues to implicate inflammation as the major coronary risk factor, such cholesterol recommendations by the NCEP may need to be modified. Although algorithms in the treatment of acute coronary events, refractory arrhythmias, and emergencies are sound practice, their appropriateness regarding prescription of statins for primary and secondary prevention takes physicians away from practicing the art of medicine.

Rather than selecting treatment options like a technician and targeting cholesterol numbers alone, physicians owe it to patients to look further into these controversial issues before embracing potent drugs that may not truly serve the needs of our patients. Although the use of statins in high-risk coronary patients, especially those with inflammatory markers, is good medicine, overuse of these potent pharmacologic agents with known and unknown side effects for long-term use in otherwise healthy people simply is not justifiable.

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