

Should All Patients with Cardiovascular Disease Receive Statin Therapy?

Based on a debate between Robert Vogel, MD, and Ernst Schaefer, MD

Debate Summary

With the strong correlation between the development of coronary heart disease and elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C), therapies that significantly lower lipid levels will be widely prescribed. Within the past 15 years, major studies have shown the statins to be very effective in lowering LDL-C levels. Are the effects of statin therapy powerful enough to justify administering one of these drugs to every patient with cardiovascular disease? Among the arguments favoring its general usage are its safety record, its high rate of patient compliance (especially in comparison to alternative therapies such as diet and exercise), and its cost effectiveness. On the other hand, elevated levels of LDL-C are not the only cause of atherosclerosis, so simply lowering the LDL-C level is not the sole answer to reducing the risk of mortality and morbidity from coronary heart disease.

Dr. Vogel:

There is incontrovertible evidence from population and intervention studies that elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) correlate with the development of coronary heart disease (CHD). Indeed, an estimated 40% of the people in the United States and Europe will die of cardiovascular disease,¹ primarily because the LDL-C levels of people who live in westernized societies are twice as high as those seen in all other animals except for the Watanabe rabbit.²

In the past 15 years, however, there has been a major revolution in primary and secondary prevention of heart dis-

ease, fueled in large part by the development of the HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors (statins), which have been very effective in lowering LDL-C levels. The statins currently available reduce plasma concentrations of LDL-C by about 20% to 60%, increase levels of high-density lipoprotein cholesterol (HDL-C) by 5% to 15%, and reduce triglyceride levels by 10% to 45%.³⁻⁵ Newer statins on the horizon appear to be even more effective in reducing LDL-C levels.

There is also increasing evidence that statins confer antiatherogenic benefits through various antiatherosclerotic and antithrombotic mechanisms that may be independent of LDL-C lowering (Table 1).^{6,7} These mechanisms may explain the clinically favorable results reported in several short-term angiographic or ultrasound studies of patients with vascular disease who received statin therapy.⁸

The central process of antiatherogenesis, however, is lowering LDL-C levels. After this is accomplished, the atherogenic potential of other lipid abnormalities, such as decreased HDL-C levels and increased levels of triglycerides and lipoprotein (a) [Lp (a)], is more or less negated. Indeed, 3 randomized secondary prevention trials—the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) trial, and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study—have shown that lowering LDL-C levels with statin therapy results in a con-

cordant average reduction in cardiovascular events of 30% at 5 years and 50% at 8 or 9 years.⁹⁻¹¹ The continuing reduction in cardiovascular events over time is a particularly crucial finding because coronary artery disease is a long-term disease. By comparison, the reduction in cardiovascular events with fibrates is only 22% at 5 years,¹² and the decrease in mortality with niacin is only 11% at 15 years,¹³ much lower than the decrease seen with statin therapy.

In addition, the beneficial effects of lowering LDL-C on cardiovascular events reported in the 4S, CARE, and LIPID studies have been strongly supported by 2 primary prevention trials—the West of Scotland Coronary Prevention Study¹⁴ and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)¹⁵—and numerous angiographic trials, the largest of which has shown a clear benefit in reducing the incidence of events for an LDL-C level of 2.5 mmol/L versus an LDL-C level of 3.6 mmol/L.¹⁶ Not only did the secondary prevention trials show a strong correlation between reductions in LDL-C levels and reductions in morbidity and mortality with statin therapy, but they also showed that these beneficial effects occur in men and women, in younger and older patients, in smokers, in patients with diabetes, and in patients with normal and elevated cholesterol levels. Most strikingly, and most importantly, is that the patients in these trials who benefited the most from statin therapy were those with cardiovascular risk factors other than elevated LDL-C and total cholesterol levels—ie,

diabetes, low HDL-C levels, and high triglyceride levels. Thus, from the clinical trial data, it is reasonable to conclude that all patients with cardiovascular disease should receive statin therapy.

The high rate of patient compliance and the safety of the statins further support the use of statin therapy. The safety record of the statins is very impressive. In various statin trials that have provided 250,000 patient-years of data, there have been no drug-induced deaths and no permanent morbidity. Compliance and safety are crucial issues because no therapy will work if patients do not adhere to it or if it causes more adverse effects than benefits.

As a class, statins are well tolerated and associated with fewer side effects and higher rates of compliance than other cholesterol-lowering interventions such as niacin, resins, and fibrates.^{17,18} In the large-scale statin trials, the side-effect profile and the discontinuation of therapy rates were similar to those of placebo, with compliance rates upwards of 90% at 1 year. In primary care settings, the probability of drug discontinuation at 1 year was only 15% with lovastatin, but 37% with gemfibrozil, 41% with resins, and 46% with niacin.¹⁸ Thus, it appears that patients not only will adhere to statin therapy, but will continue with statin therapy for a long time.

Although some experts argue that diet and exercise are alternatives to statin therapy in reducing cardiovascular morbidity and mortality, this is not a sound line of reasoning. Historically, adherence to dietary and lifestyle modifications is poor, and these modifications alone are rarely sufficient to achieve guideline lipid levels. Moreover, patients who have cardiovascular disease because of inappropriate diet and a sedentary lifestyle are often the ones who are most resistant to implementing dietary and lifestyle modifications.

Other experts will argue that revascularization is an alternative to statin therapy for managing cardiovascular disease. Even though revascularization is beneficial for patients with angina, it is not a

Table 1. Pleiotropic Effects of Statins

- Improved endothelial function
- Plaque stabilization
- Suppression of inflammation
- Decreased lipoprotein oxidation
- Improved platelet function
- Reduced blood viscosity

viable alternative for patients with other forms of coronary disease, irrespective of specific lesions.

Cost and cost effectiveness are important issues in treating and preventing cardiovascular disease, especially because there are limited resources worldwide for what is essentially a global problem. A study based on medical price levels in the United States concluded that it would be cost effective (cost less than \$50,000 per year of life saved) to intervene with statin therapy in any patient whose annual risk for coronary artery disease exceeded 1%; this includes all patients with preexisting coronary artery disease or diabetes.¹⁹ Another study estimated the costs of statin therapy to be \$8200 (about \$12,300) per year of life gained in patients with an annual risk for CHD of 3%.²⁰

Moreover, a cost comparison found that the cost per year of life saved with statin therapy in a patient at high risk for coronary artery disease is about \$5000 to \$10,000, the same as the cost of revascularization in a patient with severe angina and left main coronary artery disease.²¹ Revascularization is rarely withheld because of cost from patients requiring the procedure; therefore, all patients with coronary disease should receive a statin for both clinical and economic reasons.

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Dr. Schaefer:

Clearly, statin therapy is beneficial for many patients with cardiovascular disease. However, elevated LDL-C levels are not the only cause of atherosclerosis, so simply lowering the LDL-C level is not the sole answer to reducing the risk of mortality and morbidity from CHD.

Although approximately one third of the people with CHD have LDL-C levels above 4.1 mmol/L,²² several other factors are involved in the development of atherosclerosis, including arterial hypertension (which is twice as common in people with CHD as in those without CHD),²² cigarette smoking, low HDL-C levels, elevated homocysteine levels, elevated

triglyceride levels, elevated Lp (a) levels, and diabetes. Studies of families with premature heart disease have shown that 18% have high LDL-C levels; most have combined hyperlipidemia; and 3% have familial hypercholesterolemia. The remainder have either elevated Lp (a),

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—Robert Vogel, MD

high triglyceride and low HDL-C, or low HDL-C levels.²³ Studies have also shown that elevated LDL-C, decreased HDL-C, and elevated Lp (a) levels are independent risk factors for CHD.²⁴⁻²⁶ Whereas LDL-C levels at or above 4.1 mmol/L increase the relative risk of CHD by 74% in men and by 65% in women, HDL-C levels below 0.9 mmol/L increase the risk of CHD by 46% in men and by 100% in women, which is twice the risk.²⁷

Lowering LDL-C to goal levels with statins or other cholesterol-lowering agents is clearly important in reducing the risk for CHD. However, with so many other factors playing a role in atherogenesis, there are not enough evidence-based data to justify statin therapy for every person with an LDL-C level below 2.5 mmol/L, the US therapeutic goal, or 3.0 mmol/L, the European goal.

Angiographic trials evaluating various statins have shown decreased rates of disease progression with statins versus placebo, but these trials have not shown regression of atherosclerosis. Thus far, the only studies that have shown disease regression are those involving combination therapy.

As demonstrated in various secondary prevention trials, the statins have increased HDL-C by only 5% to 8% and

have lowered LDL-C levels by 25% to 35%, triglycerides by 10% to 14%, heart disease by 24% to 34%, and death from CHD by 20% to 42%.²⁸ If there were greater increases in HDL-C levels and greater reductions in LDL-C levels, there would be even greater reductions in cardiovascular events and death from CHD.

Importantly, at least 4 intervention trials have demonstrated that supervised dietary modification (that is, replacing saturated fat with polyunsaturated fat, butter with margarine, whole milk with skim milk, and animal fats such as lard and tallow with vegetable oils) or fish oil supplementation is effective in reducing CHD mortality (Table 2). In the 6-year Finnish Mental Hospital Study, which involved more than 10,000 individuals, replacing butter with margarine and whole milk with skim milk reduced CHD mortality by 53% in men and by 34% in women.²⁹ In the 4-year Lyon Diet Heart Study,³⁰ the popularly known “Mediterranean diet,” which is low in saturated fat and high in alpha-linoleic acid, reduced CHD mortality by 65%. In the 2 studies utilizing fish oil supplements—the Diet and Reinfarction Trial³¹ and the Gruppo Italiano per lo Studio della Sopravvivenza

nell’Infarto miocardico³²—the intervention reduced CHD mortality by 33% and 17%, respectively. As these intervention trials show, dietary modifications can be recommended as effective options in reducing mortality from CHD.

REBUTTAL

Dr. Vogel:

This debate has spawned 2 central questions: Do we want to treat lipids or do we want to treat patients? And, do we want to debate risk factors or do we want to prevent morbidity and mortality from CHD?

HDL-C and triglycerides are important factors in the development of atherosclerosis, and cholesterol-lowering agents other than statins are helpful in selected cases. However, it is interesting to see a 22% reduction in cardiovascular events in the Veterans Affairs HDL-C Intervention Trial (VA-HIT),¹² which involved the use of gemfibrozil in people with low HDL-C levels, but a 35% reduction in cardiovascular events in the AFCAPS/TexCAPS trial,¹⁵ in which lovastatin was administered to people who also had low HDL-C levels.

In addition to reducing the incidence of CHD events by reducing LDL-C and total cholesterol levels, statins decrease the incidence of stroke and transient ischemic attacks.¹⁰ Statins also reduce cognitive impairment, lower blood pressure by about 5 mm Hg,³³ and reduce the risk of fracture, including hip fracture, by about 70% after 3 years of use.^{34,35} Moreover, observational data from the Mayo Clinic show that patients on statin therapy who experience a myocardial infarction (MI) have only 20% the mortality (an 80% reduction) as do MI patients who are not on statin therapy.³⁶

Revisiting the central questions—do we want to improve lipid profiles or do we want to prevent heart disease, stroke, and other sequelae of unhealthy lifestyles—underscores the clinical benefits of statin therapy in all patients with CHD.

Table 2. Efficacy of Dietary Modification in Reducing Mortality from Coronary Heart Disease

Study	Modification	Effect on Mortality
Finnish Mental Hospital Study ²⁹	Replacement of fat with polyunsaturated fat	↓53% in men and ↓34% in women over 6 years
Lyon Diet Heart Study ³⁰	Low saturated fat and high alpha-linoleic acid diet	↓65% over 4 years
DART ³¹	Supplementation with fish oil (1-2 g/day)	↓33%
GISSI ³²	Supplementation with fish oil (1-2 g/day)	↓17%

Source: References 29-32.

DART = Diet and Reinfarction Trial; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico.

Dr. Schaefer:

Statin therapy is warranted in many patients with CHD. It is not known, however, whether an individual patient with an LDL-C level lower than 2.5 mmol/L (100 mg/dL) will benefit from such therapy. By comparison, it has been demonstrated in the VA-HIT study that patients with LDL-C levels of 2.5 mmol/L and low HDL-C levels do benefit from therapy with a fibrate, as evidenced by a 22% reduction in cardiovascular events.¹² In the CARE study, however, patients with LDL-C levels below 125 mg/dL (3.2 mmol/L) received no significant benefit (that is, they did not have fewer cardiovascular events) from therapy with pravastatin.¹⁰ AFCAPS/TexCAPS, on the other hand, was a primary prevention trial in which an LDL-C level between 130 and 190 mg/dL and an HDL-C level below 50 mg/dL were required for study entry.¹⁵

At present, the real question concerns future directions and therapeutic goal levels. European guidelines now set the LDL-C goal for high-risk patients at less than 3.0 mmol/L, but this may be lowered to less than 2.0 mmol/L (80 mg/dL) if the results of the ongoing Treating to New Targets trial are positive; nevertheless, it is likely that future trials will justify the goals of therapy listed in **Table 3**. The results of the VA-HIT¹² support HDL-C levels greater than 1.0 mmol/L; the results of the Heart and Estrogen/Progestin Replacement Study³⁷ demonstrate that hormonal replacement therapy reduces Lp (a) levels in postmenopausal women with heart disease and elevated Lp (a) levels.

Although statins are useful drugs, they are not sufficient. Other approaches are needed to prevent CHD morbidity and mortality, including supervised lifestyle modification, control of other risk factors, dietary supplementation with essential fatty acids, better therapeutic agents that raise HDL-C levels and lower Lp (a) levels, combination therapy with 2 or 3 drugs, and better angiographic assessment. For patients with homozygous familial hypercholes-

terolemia, which is largely unaffected by statin therapy, the most effective approach is LDL-C apheresis and, in the future, gene therapy.

QUESTION-AND-ANSWER SESSION**Risk Factors Other than LDL-C**

Question from the Audience: *Dr. Vogel, you suggested that the use of a statin may cancel out the atherogenicity of other risk factors, such as decreased HDL-C levels. Can we truly play down advising patients to raise their HDL-C levels or to lose weight if they are taking an appropriate dose of a statin for an appropriate length of time?*

Dr. Vogel: My honest opinion is that we need to do everything we can. As I mentioned earlier, 40% of us in the United States and Europe will die of cardiovascular disease.¹ Putting our polarized viewpoints aside for a moment, I think that other approaches are appropriate; however, the proof that these other approaches are feasible, particularly in terms of compliance, is scant.

The wonderful thing about the statins is that they have a profound effect on LDL-C, and secondarily on very low-density lipoproteins, both of which are prerequisites for atherosclerosis. I believe that if all of us had an LDL-C level below 80 or 100 mg/dL, the remaining risk factors for cardiovascular disease would be greatly attenuated and 90% of coronary events would be prevented.

Table 3. Therapeutic Goal Levels

- LDL-C < 2.0 mmol/L (80 mg/dL)
- HDL-C > 1.0 mmol/L (40 mg/dL)
- Triglycerides < 1.7 mmol/L (150 mg/dL)
- Lipoprotein (a) < 30 mg/dL

LDL-C = low-density lipoprotein cholesterol;
HDL-C = high-density lipoprotein cholesterol.

Dr. Schaefer: I wish it were true, but that is not the case. In my clinic, I frequently encounter patients who work very hard to reduce their LDL-C levels, but their HDL-C levels are still in the neighborhood of 25 mg/dL and their Lp (a) levels are still elevated. When these patients come in, the first thing you see is the abdomen. Despite an LDL-C level below 100 mg/dL, they also have type 2 diabetes and angina. If they've had a coronary bypass, they're developing angina again, and they need to be reevaluated by a cardiologist. Although the statins are very good drugs, they have not eradicated heart disease, which is a complex disease requiring further study.

Dr. Vogel: Data from the Framingham Heart Study indicate that there have been only 6 MIs over the past 52 years in the town of Framingham in patients with total cholesterol levels below 4 mmol/L and LDL-C levels below 2.5 mmol/L (Personal communication, R.A. Vogel and W. Castelli).

Dr. Schaefer: That's true, but the population in Framingham is very small.

Diet and Exercise

Member of the Audience: I would like to add a comment about supervised lifestyle changes. About 2 years ago, the New England Journal of Medicine published the results of a 1-year study in which 400 patients participated in an intensive, supervised sports and dietary program. The dietary changes were in accordance with National Cholesterol Education Program II guidelines. After 1 year, there was a significant reduction in LDL-C of 0.5 mmol/L or 20 mg/dL.

Dr. Schaefer: Yes, and I am pleased to add that people who exercise regularly enjoy other benefits in addition to lower LDL-C levels and reduced risk for CHD. They have a lower incidence of depression and a lower suicide rate, and they live, on average, 3 years longer.³⁸

The point is that we have to do everything we can, particularly because these

approaches are not mutually exclusive. It is not enough for a cardiologist to tell a patient, "Just take a statin and we won't have to worry about anything else." There are other factors about which to be concerned.

Dr. Vogel: The reason cardiologists say that is because they know statins work and lifestyle modifications are difficult to stay with in the long run. I serve on a panel that oversees a project under which Dr. Dean Ornish's \$12,000 diet and exercise program is made available free of charge to Medicare recipients in the United States. In the past year since we have been advertising the availability of the program, only 2 people have enrolled.

I think the diet is wonderful, but I have a body mass index of 22 and I probably will not develop heart disease. However, the people who would benefit most from the program—those who don't have a body mass index of 22, who don't exercise, but who do develop heart disease—are not likely to follow such a program, let alone enroll.

Statin Use in Hypertensive Patients

Question from the Audience: Dr. Vogel, in light of the relationship between low cholesterol, hypertension, and the risk of hemorrhagic stroke, would you prescribe a powerful statin for a patient with cardiovascular disease and hypertension but a normal cholesterol level? Is there a downside to "one size fits all" therapy?

Dr. Vogel: That is a very good question. Based on the data available thus far, none of the statin trials that have looked at hemorrhagic stroke has found any increase in incidence. In this regard, the statins are very safe drugs, and I would not hesitate to prescribe them for patients with cardiovascular disease and hypertension.

However, the definition of normal cholesterol is subject to interpretation. I would define normal cholesterol as an LDL-C level below 100 mg/dL or 2.5 mmol/L and an HDL-C level above 40 mg/dL or 1 mmol/L.

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