

PETITION TO THE NATIONAL INSTITUTES OF HEALTH
SEEKING AN INDEPENDENT REVIEW PANEL TO RE-EVALUATE
THE NATIONAL CHOLESTEROL EDUCATION PROGRAM GUIDELINES

September 23, 2004

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Director, National Institutes of Health

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Dear Sirs and Madam,

On July 12, 2004, the National Cholesterol Education Program of the National Heart, Lung and Blood Institute issued updated recommendations for “cholesterol management”¹ based on five studies released since the 2001 update of treatment guidelines.

The new NCEP report lowers the threshold for considering statin therapy. According to this report, people at moderately high risk of developing, but no previous history of heart disease (“primary prevention”) and LDL-cholesterol levels between 100 and 129 mg/dL should now be offered the “therapeutic option” of cholesterol-lowering therapy with a statin. Similarly, statin therapy should now be offered to very high risk patients, those who already have heart disease (“secondary prevention”), when their LDL levels are between 70 and 100 mg/dL. The new recommendations apply to both men and women regardless of age. Based on these new thresholds, millions more Americans now fall within the eligibility criteria for statin therapy.

These recommendations have been criticized by some observers because the initial report published in *Circulation* failed to disclose that eight of its nine authors have

financial relationships with drug companies.² These conflicts of interest were, therefore, not included in most of the initial widespread media reports about the report and became the primary focus of concern. Such conflicts certainly could affect authors' judgment and undermine public confidence in the report. We urge NHLBI to avoid such conflicts in the future. But like surrogate endpoints in clinical studies, the conflicts are a diversion from the most important question: Are these lower LDL targets justified by the scientific evidence?

Even accepting the manufacturers' interpretation of the data from their own studies at face value (without access to the raw data), our analysis shows that several of the NCEP's recommendations are not supported by the latest evidence. We recognize that the studies we discuss below were underpowered to demonstrate statistically significant effects in certain population sub-groups. Moreover, we do not argue that controlled studies are needed to evaluate the effects of treatment regimens on every imaginable sub-group, especially if it appears that the underlying biology is similar for all sub-groups. But when the results for a sub-group run counter to the study as a whole, it is not appropriate to conclude that the study has shown the proposed therapy has benefits for that sub-group.

Therefore, we, the undersigned, are petitioning the NHLBI's NCEP to create an independent review panel free of conflicts of interest to review all the data in the five studies that led to this recent update. It should also review the studies that led to the original guidelines. If warranted, it should issue revised conclusions.

We believe the evidence does not support extending these guidelines to women who are at moderately high risk of CVD (so-called "primary prevention").

The 2001 guidelines cited six references³ as evidence that statins reduce the risk of heart disease in moderately high risk women under the age of 65.⁴ Not one of the six studies, however, provides significant evidence to support this claim. In a later section, the guidelines admitted that studies supporting this recommendation "generally are lacking" (meaning they don't exist), and that the recommendation "is based on extrapolation of benefit from men of similar risk."⁵

Among the five new studies, only ASCOT specifically addresses the benefit of statin therapy in women with multiple risk factors and no history of heart disease.⁶ In this study, the women treated with atorvastatin developed 10 percent *more* heart disease (not significant) than the women in the control group. Therefore, there is still no significant evidence from the “gold standard” of medical research, large randomized clinical trials, showing that women who do not already have heart disease benefit from taking a statin drug.

We believe the evidence does not support extending these guidelines to older persons who are at risk of CVD (primary prevention).

For people above the age of 65 without heart disease, the 2001 guidelines cited nine references to support the claim that statin therapy effectively reduces their risk of developing heart disease.⁷ Again, not one of the nine studies provided significant evidence that statins protect senior citizens without heart disease.

Among the latest five studies, only PROSPER looked specifically at this issue.⁸ It included more than 3,000 people between the ages of 70 and 82 at elevated risk of, but without, heart disease. The latest NCEP report states that the results of the PROSPER study “support the efficacy of statin therapy in older, high-risk persons without established CVD.” In fact, the evidence shows just the opposite. Those treated with a statin did not experience significantly fewer heart attacks and strokes. But they did develop 25 percent more new cancers than the people in the control group (statistically significant). Although the published study does not divide the new cancer diagnoses into primary- or secondary-prevention patients, it is worrisome that the risk grew each year a statin was taken, so that by the fourth year of the study there was more than one additional case of cancer for each 100 patients taking a statin for a year.

To downplay this increased cancer risk, the NCEP report relied upon the same logic as the original PROSPER study: when its data are merged with data from previous statin clinical trials in a meta-analysis, the increased cancer risk is reduced to insignificance. However, this argument was flawed because it merges studies that included younger populations (mean age < 60)⁹ with the PROSPER patients, who were all 70 and above.

We believe the evidence in the five latest clinical trials for extending these guidelines to primary prevention of coronary heart disease in patients with diabetes is mixed.

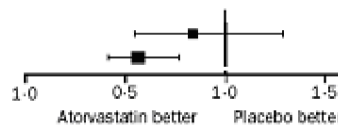
For diabetic patients, the new recommendations cite the Heart Protection Study’s finding that statins significantly reduce the risk of heart disease, even among those without heart disease.¹⁰ However, this ignores the three other studies under review that found that statins did not provide significant benefit to people with diabetes.^{11 12 13}

DIABETES

ASCOT (Risk of fatal and non-fatal heart attack)

Subgroups

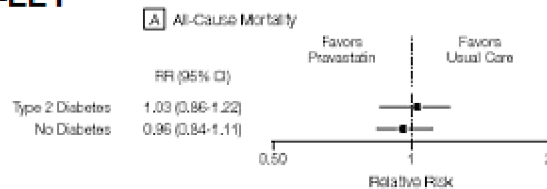
Diabetes
Non-diabetes



PROSPER (Risk of heart attack or stroke)

	Placebo		Pravastatin		Hazard ratio (95% CI)
	Total number	Number with event (%)	Total number	Number with event (%)	
History of diabetes					
No	2503	414 (16.0)	2588	338 (13.1)	0.79 (0.60-0.91)
Yes	320	59 (18.4)	303	70 (23.1)	1.27 (0.90-1.80)

ALLHAT-LLT



Furthermore, taking the HPS findings at face value, one death was prevented each year that 250 diabetic patients were treated with a statin. For comparison, an observational study reported that if 250 sedentary diabetic patients become physically active, four times as many lives will be saved¹⁴—though the relative importance of statin therapy and routine exercise was not mentioned in the NCEP recommendations.

We believe that the results of the ALLHAT study did not show a benefit from more than tripling the number of people taking statins (as recommended by the 2001 and 2004 NCEP updates)

In ALLHAT, patients at increased risk of heart disease were randomized to receive statin therapy or to be treated by their regular doctor according to the community standards of the mid-1990s. Serendipitously, about 3 times as many people in the treatment group as in the “regular care” group ended up on statin therapy — almost a perfect test of the recommendation to triple the number of Americans taking statins that was later made in the 2001 NCEP guidelines.

The results show that tripling the number of people taking statins (virtually in accord with the recommendations of the 2001 NCEP recommendations) provides no additional benefit—not to those older or younger, male or female, with or without diabetes, with or without heart disease, and among those without heart disease, not to those with LDL-cholesterol higher or lower than 130 mg/dL. The only group that derived any significant benefit from more statins was African-Americans, who had fewer episodes of heart disease, but not fewer deaths. In other words, the people in the ALLHAT study treated in accord with the 2001 guidelines did no better than the people who were treated more in accord with the 1993 guidelines. The ALLHAT study suggests that treating an additional 25-30 million Americans with statins as suggested by the 2001 and latest NCEP recommendations will provide little, if any, benefit. This evidence certainly does not justify adding tens of billions of dollars to our annual health care expenditures.

In petitioning for an independent review, we are not arguing that statins are not helpful for many people with elevated risk of heart disease. However, there is strong evidence to suggest that an objective, independent re-evaluation of the scientific evidence from the five new studies of statin therapy would lead to different conclusions than those presented by the current NCEP.

In this letter we have focused on the recommendations for primary prevention because the discrepancies between the studies cited and the recommendations made are so clear. We also believe that the recommendations for secondary prevention should be

re-evaluated with particular attention to comparisons between the effectiveness of statins compared to lifestyle changes and the number of patients that must be treated to help one (so-called “number needed to treat” or NNT).

While the latest NCEP report, like the 2001 guidelines before it, notes that lifestyle modification should be a first line of therapy to prevent heart disease, the sad fact is that these recommendations are being largely ignored, partly because the “experts,” many of whom have conflicts of interest through their relationships with statin manufacturers, focus ever more attention on lowering cholesterol with expensive drugs. The vast majority of heart disease can be prevented by adopting healthy habits.

The American people are poorly served when government-sanctioned clinical recommendations, uncritically amplified by the media, misdirect attention and resources to expensive medical therapies that may not be scientifically justified. Only an independent review, totally free from conflicts of interest, can restore public confidence by determining if that has happened in this case. We therefore request that you move expeditiously to appoint such a panel and provide it with the resources needed to conduct the review.

Sincerely,

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¹ Grundy SM, Cleeman JI, Merx NB, et al. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227-239.

² http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3upd04_disclose.htm accessed 9/04/04.

³ NCEP Full Report, p II-5.

⁴ NCEP Full Report, p. II-3.

⁵ NCEP Full Report, VIII-3.

⁶ Sever PS, Dahlof B, Poulter NR, et al. Prevention Of Coronary And Stroke Events With Atorvastatin In Hypertensive Patients Who Have Average Or Lower-Than-Average Cholesterol Concentrations, In The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): A Multicentre Randomised Controlled Trial. *Lancet*. 2003;361:1149-1158.

⁷ NCEP Full Report, p. II-5.

⁸ Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER): A Randomized Controlled Trial. *Lancet*. 2002;360:1623-1630.

⁹ Bjerre LM, LeLorier J. Do Statins Cause Cancer: A Meta-analysis of Large Randomized Clinical Trials. *American Journal of Medicine*. 2001;110:716-723.

¹⁰ Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of Cholesterol-Lowering with Simvastatin in 5963 People with Diabetes: A randomized Placebo-Controlled Trial. *Lancet*. 2003;361:2005-2016.

¹¹ Sever PS, op. cit..

¹² Shepherd J, op.cit.

¹³ The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual Care. *Journal of the American Medical Association*. 2002;288:2998-3007.

¹⁴ Gregg EW, Gerzoff RB, Caspersen CJ, et al. Relationship of Walking to Mortality Among US Adults with Diabetes. *Archives of Internal Medicine*. 2003;163:1440-1447.