Benefits of lipid lowering on vascular reactivity in patients with coronary artery disease and average cholesterol levels: A mechanism for reducing clinical events?

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Background The favorable effects of lowering low-density lipoprotein (LDL)-cholesterol on reducing clinical events in patients with coronary disease have been well established. The mechanisms responsible for this benefit, however, have not been fully understood. This study examined the impact of lipid-lowering therapy on endothelium-dependent vasoreactivity in a subgroup of patients after myocardial infarction with average cholesterol levels who participated in the Cholesterol Recurrent Events (CARE) study to determine whether an effect on endothelial function is a viable mechanism for the observed reduction in clinical events.

Methods and Results Participants were recruited from among volunteers in the CARE trial at 2 university-based outpatient cardiology clinics. Patients were randomly assigned to pravastatin or placebo. Plasma lipids were measured at baseline and semiannually thereafter. During the final 6 months of the trial, vasoreactivity was assessed by change in ultrasound-determined brachial artery diameter in response to blood pressure cuff-induced ischemia (endothelium-dependent) and to nitroglycerin, a direct vasodilator. Differences in response were examined between the 2 randomized groups. The relation between change in LDL-cholesterol from baseline to year 5 and the magnitude of endothelium-dependent vasodilation also was examined. There was significantly greater endothelium-dependent vasodilation observed in the pravastatin group compared with the placebo group (13% vs 8%, $P = .0002$), with no difference between the groups in their response to the endothelium-independent vasodilator nitroglycerin. The magnitude of the endothelium-dependent vasodilation was significantly correlated with the percent change in LDL-cholesterol from baseline to final visit ($r = 0.49$, $P = .015$).

Conclusions These findings indicate that the use of pravastatin in patients after myocardial infarction with average cholesterol levels is associated with greater endothelium-dependent vasodilation compared with those who received placebo. The magnitude of this vasodilatory response is correlated to the reduction in LDL-cholesterol. This improvement in endothelium-dependent vasoreactivity may be a likely mechanism, at least in part, for the reduction in recurrent clinical events observed and reported in the CARE study. (Am Heart J 2000;139:734-8.)

During the decade of the 1990s, a large body of evidence from well-designed, randomized clinical trials has documented the benefits of lowering blood levels of low-density lipoprotein cholesterol (LDL-C) in reducing cardiovascular events, not only among patients with clinical coronary disease but also among those with little or no evidence of disease.[1-5] The results of these studies as well as those from prior smaller-scale trials that focused on the rate of atherosclerotic disease progression have spurred great interest in understanding the mechanisms for the observed clinical benefit.[6,7] One widely held theory is that lowering LDL-C reduces the lipid content of the atherosclerotic plaque, resulting in more stable lesions and thereby reducing the likelihood of plaque rupture, which is a frequent cause of clinical events.[8-13] This mechanism, however, does not explain other important findings, particularly the reduction in myocardial ischemia that has been observed.[10-13] Therefore other mechanisms, not mutually exclusive, must be considered to explain the clinical benefits observed.

Patients with hypercholesterolemia and/or atherosclerotic disease have been shown to have impaired endothelium-dependent vasodilation.[14,15] This abnor-

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Table I. Demographic, baseline, and on-treatment lipid Levels for vasoreactivity subgroup and for all CARE participants by randomized assignment

	Vasoactivity subgroup		CARE (all)	
	Placebo (n = 18)	**Pravastatin (n = 18)**	**Placebo (n = 2078)**	**Pravastatin (n = 2081)**
Demographic data and baseline lipid levels				
Age (y)	60	62	59	59
M/F	14:4	16:2	86% men	86% men
Total cholesterol (mg/dL)	210 ± 18	210 ± 19	209 ± 17	209 ± 17
LDL-C (mg/dL)	141 ± 15	140 ± 14	139 ± 15	139 ± 15
HDL-C (mg/dL)	42 ± 11	44 ± 9	39 ± 61	39 ± 9
Triglycerides (mg/dL)	139 ± 40	133 ± 30	155 ± 61	156 ± 61
On-treatment lipid levels				
Total cholesterol (mg/dL)	219 ± 31	163 ± 23*	209	167†
LDL-C (mg/dL)	138 ± 28	94 ± 18*	136	98†
HDL-C (mg/dL)	42 ± 11	45 ± 8	39	41†
Triglycerides (mg/dL)	197 ± 105	120 ± 46†	156	134†

*$P < .0001$ (vs placebo).
†$P < .01$ (vs placebo).

mality in endothelial function may be important in promoting the atherosclerotic process and in triggering clinical sequelae. Prior studies have shown a beneficial effect of LDL-C lowering, and it has been suggested that an additional mechanism for the clinical benefit may be related to the favorable effects of LDL-C lowering on impaired endothelium-dependent vasodilation that has been observed in such patients.[10-13]

The Cholesterol and Recurrent Events (CARE) trial was a double-blind, randomized, placebo-controlled trial designed to examine the effects of lowering LDL-C levels on recurrent cardiovascular events in patients after myocardial infarction with average baseline cholesterol levels. The pravastatin-treated group had a 24% reduction in the primary end point ($P = .003$) (fatal coronary events plus recurrent nonfatal myocardial infarctions) compared with the placebo group.[2] The CARE trial afforded a unique opportunity to study the effects of long-term lipid-lowering therapy on endothelium-dependent vasoreactivity among patients with documented coronary heart disease and average baseline cholesterol levels by comparing the 2 randomized groups. In addition, the relation between the percentage lowering of LDL-C and the magnitude of endothelium-dependent vasodilation was assessed.

Methods

Thirty-six active participants were recruited from 2 clinical sites during the last 6 months of the trial. These patients were recruited for this substudy on the basis of their final visit schedules and were not otherwise preselected. All data were collected and analyzed before the unblinding of study personnel and the participants.

Subjects were studied in the supine position after a 10-minute rest period with imaging apparatus in place. Vasoactive medications were held for 12 to 24 hours. Brachial artery diameters were measured noninvasively in the nondominant arm by high-resolution B-mode ultrasonography. After 2 resting ultrasound images were obtained, a pneumatic tourniquet on the upper arm was inflated to 50 mm Hg above resting systolic pressure, maintained for 3 minutes, and released. Continuous imaging of the brachial artery was performed for 90 seconds followed by a 10-minute rest period and repeat baseline images. Sublingual nitroglycerin was then given, and images were recorded for 5 minutes. This method has been well described.[15,16]

Table II. Brachial artery diameter at baseline and percent diameter change after cuff inflation and after nitroglycerin administration by randomization group

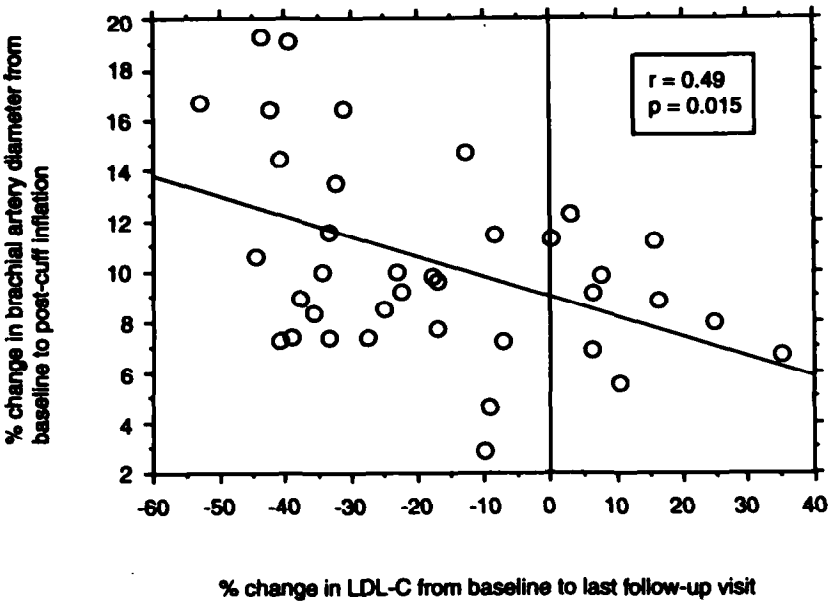
	Placebo (n = 18)	**Pravastatin (n = 18)**
Baseline brachial artery diameter (mm)	4.4	4.5
Change from baseline diameter (%)		
After cuff inflation	8 ± 2	13 ± 4*
After nitroglycerin	16 ± 6	15 ± 9

*$P = .0002$ (vs placebo).

Endothelium-dependent vasoreactivity was assessed by measuring change in brachial artery diameter 1 minute after termination of the arterial occlusion compared with the baseline measurement. Endothelium-independent vasodilation was assessed by measurement of change in brachial artery diameter 4 minutes after the administration of nitroglycerin compared with baseline measurement. The changes thus measured were expressed as percent baseline diameter.

The same study personnel collected all imaging data on all patients at both sites. Measurement variability was assessed by reanalyzing the precuff inflation data. The two means were 4.74 ± 0.822 mm and 4.52 ± 0.777 mm, respectively, and the estimated coefficient of variation was 1.5%, similar to previously published reports.[15,16]

Figure 1



Relation between LDL-C change and endothelium-dependent vasodilation (both subgroups combined, n = 36).

Plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured by the core lipid laboratory at baseline and at regular predetermined intervals throughout the trial. The baseline and final visit measurements were used to calculate the percentage change in plasma LDL-C. Study personnel were blinded to the lipid data as well as to drug group assignment.

The study was approved by the institutional review board at each clinical center. All volunteers gave written informed consent.

Results

Among the 36 patients studied, there were no differences between the placebo-treated and pravastatin-treated groups in baseline systolic and diastolic blood pressures or resting heart rate. The demographic data as well as the baseline and final lipid levels for the placebo and pravastatin groups are shown in the top panel of Table I. The groups were equal in number and comparable in age, sex, and baseline lipid levels. The baseline data for this subgroup are similar to that of the entire CARE cohort, the data for which are also shown in Table I for comparison. When considering postrandomization lipid levels, the magnitude of the change from baseline in each study subgroup and the difference in the on-treatment lipid levels between the two subgroups are similar to the entire CARE cohort. The on-treatment lipid levels for the study subgroup and for all CARE participants are shown in the bottom panel of Table I.

The baseline resting brachial artery diameter was similar in both the placebo and pravastatin groups (Table II). The pravastatin-treated group had a significantly greater increase in brachial artery diameter after cuff inflation than did the placebo group (13% ± 4% vs 8% ± 2%, $P = .0002$). After nitroglycerin was given there was no significant difference in brachial artery diameter between the two randomized groups (16% ± 6% vs 15% ± 9%). These data are shown in Table II.

The relation between percent change in LDL-C from baseline to follow-up and the magnitude of the brachial artery vasodilation in response to cuff-induced hyperemia was examined in all 36 patients. As shown in Figure 1, there was a significantly positive correlation between plasma LDL-C reduction and the magnitude of the endothelium-dependent vasodilatory response ($r = 0.49$, $P = .015$).

Discussion

This study demonstrates that patients after myocardial infarction with average cholesterol levels treated with pravastatin had significantly greater flow-mediated, endothelium-dependent vasodilation than did the placebo-treated group. As expected, there was no difference between the groups in the response to nitroglycerin, a vasodilator that directly affects smooth muscle cells. No studies of vascular reactivity were performed before random assignment, but there is no reason to

believe the two groups were different because all other characteristics were similar at baseline and the two groups were randomly assigned. The two study subgroups also appear to be representative of the overall CARE cohort.

Previous studies of coronary arteries as well as the peripheral arteries have used a variety of endothelium-dependent vasodilators and flow-mediated shear stress. These studies have shown that the vasodilation is mediated by local release of nitric oxide, the generation of which is impaired in a variety of conditions including hypercholesterolemia and atherosclerosis.[17-21] In addition, a significant correlation has been shown between coronary and brachial artery endothelium-dependent vasodilation in patients with or without coronary artery disease.[22]

The beneficial effect of lipid lowering on coronary artery endothelium-dependent vasodilation has been previously shown.[23-25] The effect of lipid lowering on vasoreactivity also has been studied in a group of healthy middle-aged men with a mean baseline LDL-C of 133 mg/dL.[26] After only 2 weeks of simvastatin treatment LDL-C fell to 88 mg/dL, and a significant improvement in flow-mediated brachial artery vasoreactivity was observed, providing evidence that endothelial function can be improved in healthy individuals with above-optimal serum LDL-C when treated to levels below the National Cholesterol Education Program current guidelines.

An even more rapid improvement in endothelium-dependent vasodilation with LDL-C reduction was documented by Tamai et al.[27] Forearm blood flow was studied with the use of string-gauge plethysmography; acetylcholine and sodium nitroprusside were infused both before and after a single LDL-C apheresis session, which reduced LDL-C from 142 to 32 mg/dL. Forearm blood flow improved significantly after apheresis with acetylcholine infusion and was unchanged with nitroprusside. The rapidity of improvement suggests that higher levels of LDL-C may directly impair endothelial function, perhaps by a reduction in nitric oxide availability, and is consistent with the results of another study that showed that a single high-fat meal can rapidly reduce endothelium-dependent vasodilation in healthy individuals.[28]

Data from the current study show a significant correlation between the magnitude of the LDL-C reduction and the magnitude of endothelium-dependent vasodilation. A previously reported study suggests that after 1 year of treatment with lovastatin and probucol, improved endothelium-dependent coronary vasodilation correlated most closely with the reduction of oxidized LDL-C.[29] Another study showed that blunted endothelium-dependent vasodilation after a high-fat meal could be attenuated by 1000 mg of vitamin C and 800 IU of vitamin E. The authors suggest that postprandial lipemia is one factor responsible for the blunted endothelial response, and the favorable effects of the antioxidant vitamins suggest an antioxidant mechanism. The role of antioxidants was not examined in the current study.

The results of this study demonstrate that cholesterol lowering with pravastatin improves brachial artery endothelium-dependent vasodilation in patients after myocardial infarction with average levels of cholesterol. The findings are consistent with the hypothesis that the benefit in reducing recurrent cardiovascular events in the CARE study may be caused, at least in part, by improvement in endothelial function as a result of LDL-C reduction.

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