# Coronary Artery Disease Prognosis and C-Reactive Protein Levels Improve in Proportion to Percent Lowering of Low-Density Lipoprotein

James H. O'Keefe, Jr., MD[a,*], Loren Cordain, PhD[b], Philip G. Jones, MS[a], and Hussam Abuissa, MD[a]

**This editorial outlines the data supporting aggressive lipid goals and options for treating low-density lipoprotein (LDL) cholesterol to a range of approximately 30 to 70 mg/dl. The physiologically normal cholesterol range is approximately 30 to 70 mg/dl for native hunter-gatherers, healthy human neonates, free-living primates, and virtually all wild mammals. Randomized statin trials in patients with recent acute coronary syndromes and stable coronary artery disease have demonstrated that cardiovascular events are reduced and cardiovascular survival optimized when LDL cholesterol is reduced to <70 mg/dl. Secondary prevention trials have shown a decrease in all-cause mortality in proportion to the magnitude of LDL cholesterol reduction. An original analysis of available data shows that the ability of a lipid-lowering therapy to reduce the C-reactive protein level is closely correlated with its efficacy in LDL cholesterol reduction. Randomized trial data have shown no relation between either percentage LDL cholesterol decrease or final LDL cholesterol level achieved and the risk for myopathy or hepatic transaminase elevations associated with statins. Therefore, intensive LDL cholesterol reduction to levels of 30 to 70 mg/dl should be pursued in subjects with or at high risk for coronary artery disease.**  **(Am J Cardiol 2006;98: 135–139)**

The development and progression of atherosclerosis is a complicated process that is influenced by a variety of risk factors. One of these, elevated low-density lipoprotein (LDL) cholesterol appears to be a requisite catalyst in atherosclerosis, and incontrovertible evidence shows that lowering very high LDL cholesterol levels markedly reduces the risk for coronary artery disease (CAD) and its complications.[1] However, atherosclerosis is commonly seen even in asymptomatic subjects with LDL cholesterol levels of approximately 90 to 130 mg/dl, which are considered average or "normal."[1] In fact, 80% of total CAD events occur in subjects with LDL cholesterol levels in the "average" range.[2] This editorial discusses the evidence and rationale for reducing LDL cholesterol to the physiologically normal range of 30 to 70 mg/dl.

In 2004, an update to the Third National Cholesterol Education Program Adult Treatment Panel guidelines stated that the aggressive reduction of LDL cholesterol to <70 mg/dl was an optional goal for very high-risk patients.[3] However, most eligible patients are not being treated to the new aggressive goal, although safe and effective pharmacologic options are now available. A recent national survey[4] of United States physicians reported that of 1,447 treated dyslipidemic patients with CAD, 1,082 (82%) met criteria for very high risk, yet just 60% were treated to the LDL cholesterol goal of <100 mg/dl, and only 18% were treated to the new goal of <70 mg/dl.

## Why Average Is Not Optimal

An accumulating body of evidence indicates that the physiologically normal LDL cholesterol level for the average subject, and the threshold for atherogenesis and CAD events, is approximately 30 to 70 mg/dl.[1] However, the average LDL cholesterol level in American adults is approximately 130 mg/dl, or roughly twice the truly normal physiologic range.[1]

Our lifestyle today is radically different from the lifestyle for which we are genetically adapted. Hunter-gatherer populations, following their indigenous lifestyles, have shown no evidence of atherosclerosis on the basis of clinical data and/or autopsy studies.[5] These hunter-gatherers had total cholesterol levels of approximately 100 to 140 mg/dl, corresponding to LDL cholesterol levels of about 50 to 70 mg/dl. Approximately 10,000 years ago, with the introduction of agriculture and animal husbandry, the human diet and lifestyle began to change drastically.[6] Today, most American adults are overweight and sedentary, and 75% of the calories we consume are in the form of highly processed foods. Although the LDL cholesterol levels of healthy neonates are in the 30 to 70 mg/dl range, levels begin to

[a]Mid America Heart Institute, Kansas City, Missouri; and [b]Department of Health and Exercise Science, Colorado State University, Fort Collins, Colorado. Manuscript received November 14, 2005; revised manuscript received and accepted January 11, 2006.

* Corresponding author: Tel: 816-931-1883; fax: 816-756-3645.
*E-mail address:* jhokeefe@cc-pc.com (J.H. O'Keefe).

0002-9149/06/$ – see front matter 
doi:10.1016/j.amjcard.2006.01.062

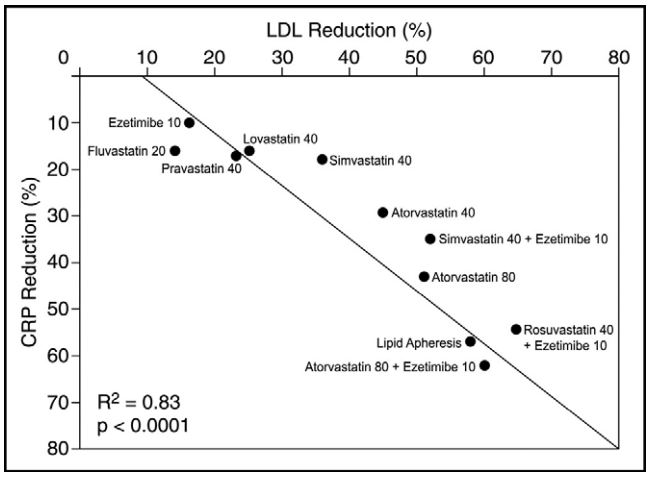


Figure 1. A highly significant relation exists between LDL cholesterol reduction and CRP reduction in randomized trials of various lipid-lowering therapies.

increase sharply as soon as infants are weaned and introduced to the modern diet.

Some physicians and patients believe that a target LDL cholesterol level of 30 to 70 mg/dl is excessively low and may predispose to adverse effects over the long term. However, this is precisely the normal range for patients living the lifestyle and eating the diet for which we remain genetically adapted. Recent studies suggest that lowering the LDL level to <70 mg/dl is not only safe but also more effective in preventing atherosclerosis and cardiovascular events than less aggressive LDL cholesterol reductions.[7]

## Lower Is Better

It is the degree to which LDL cholesterol is reduced, not the means of achieving lower levels, that determines how effectively atherosclerosis and its complications are prevented. Even in the prestatin era, studies showed that atherosclerosis progression and cardiovascular events could be reduced if LDL cholesterol was significantly reduced.[8,9] More recently, randomized controlled trials have shown that whether patients are given statins or placebo, the rate of angiographic progression of atherosclerosis is closely related to the degree of long-term reduction in LDL cholesterol.[1] Studies using ultrasound to determine carotid intimal-medial thickness as a marker for atherosclerosis have also documented that aggressive LDL cholesterol reduction halts or slows the progression of atherosclerosis, whereas moderate LDL cholesterol reduction does not.[10,11]

An intravascular ultrasound study of 507 patients showed that rosuvastatin 40 mg/day lowered LDL 53% and increased HDL 15%. At the end of 2 years, the rosuvastatin therapy regressed the coronary atheroma volume of 7%.[12] The Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: A Magnetic Resonance Imaging Observation study[12] was among the first to use high-resolution magnetic resonance imaging to assess the effects of a statin on atherosclerotic plaque size and composition. This 2-year trial randomized patients with carotid atherosclerosis to either low-dose (5 mg) or high-dose (40 or 80 mg) rosuvastatin, which resulted in LDL cholesterol reductions of 39% and 58%, respectively. Low- and high-dose statin therapy decreased the volume of plaque with a lipid-rich (proinflammatory) necrotic core by 17.6% ($p$ = NS) and 35.5% ($p$ = 0.006), respectively. These preliminary results were presented at the 75th European Atherosclerosis Society Congress in 2005.

## Low-Density Lipoprotein Cholesterol and Inflammation

Multiple studies have demonstrated that C-reactive protein (CRP), a systemic marker of inflammation, provides powerful cardiovascular prognostic information that is independent and additive to that provided by the LDL cholesterol level.[13] A highly significant relation exists whereby the more effective therapies for reducing LDL cholesterol also tend to produce the greatest reductions in CRP (Figure 1).

For example, a recent report[14] found that in subjects aged <65 years, simvastatin reduced LDL cholesterol by 38% and CRP by 16%, whereas a combination of simvastatin and ezetimibe reduced LDL cholesterol and CRP by 52% and 27%, respectively. Combination therapy with rosuvastatin and ezetimibe has produced impressive reductions in LDL cholesterol (65%) and CRP (54%).[15] Thus, more robust LDL cholesterol reductions are correlated with lower CRP levels.

## Cholesterol Reduction for Preventing Coronary Artery Disease Events

Many observational studies have demonstrated a positive relation between cholesterol levels and CAD risk that extends far below the average range noted in modern populations.[2]

The Pravastatin or Atorvastatin Evaluation and Infection Therapy trial[16] randomized 4,162 patients with acute coronary syndrome to either atorvastatin 80 mg/day or pravastatin 40 mg/day. Atorvastatin reduced LDL cholesterol by 51% to a median value during treatment of 62 mg/dl, whereas pravastatin reduced LDL cholesterol by 22% to a median level of 95 mg/dl. After 2 years, a highly significant 16% reduction in the primary end point was seen in the atorvastatin group versus the pravastatin group ($p$ = 0.005). There was also a 28% reduction in all-cause mortality ($p$ = 0.07) in atorvastatin-treated patients, although the mean LDL cholesterol level achieved in the pravastatin-treated cohort was less than the previous LDL cholesterol goal of <100 mg/dl.

The Treating to New Targets trial[17] provided support for the "lower is better" hypothesis in patients with stable CAD. In this study, 10,001 patients with stable CAD were randomized to either 80 or 10 mg/day of atorvastatin. The mean LDL cholesterol during treatment was 77 mg/dl in the

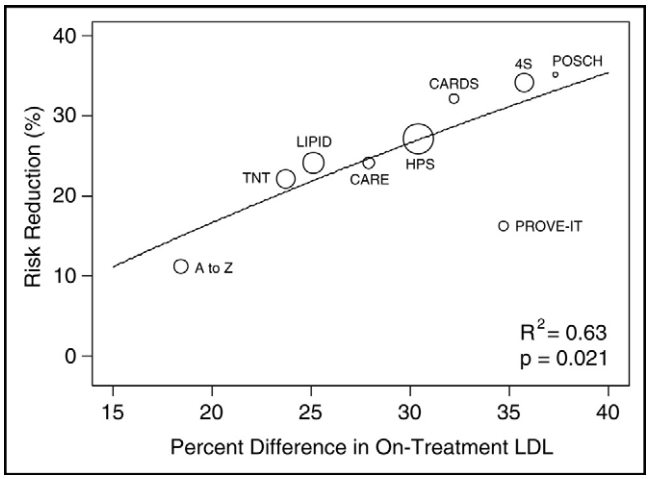


Figure 2. Relative risk reduction in CAD event rates is directly proportional to percentage difference in LDL cholesterol during treatment. Estimates were obtained from a random-effects metaregression of log hazard ratios on percentage difference in mean LDL cholesterol during treatment. The sizes of the data points are proportional to the amount of information available for each estimate; variances of effect estimates were approximated from published confidence intervals. p Values denote the significance of the slope term. The regression equation was back-translated to the (multiplicative) risk reduction scale, giving a slight curvature to the trend line in the figure. All analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). A to Z = Aggrastat to Zocor; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events; 4S = Scandinavian Simvastatin Survival Study; HPS = Heart Protection Study; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease; POSCH = Program on Surgical Control of Hyperlipidemias; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy; TNT = Treating to New Targets.

atorvastatin 80-mg arm compared with 101 mg/dl in the atorvastatin 10-mg arm. At 4.9 years of follow-up, a 22% relative reduction in events was noted in the atorvastatin 80-mg arm ($p < 0.001$).

The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering study[18] compared atorvastatin 80 mg with simvastatin 20 mg in 8,888 patients with CAD over a 5-year period during which the LDL cholesterol levels during treatment were 81 mg/dl (a 49% reduction) and 104 mg/dl (a 33% reduction), respectively. Although the primary end point was not met (major CAD events were 11% lower in the atorvastatin group, $p = 0.07$), the high dose of atorvastatin did significantly reduce the risk for stroke and nonfatal myocardial infarction. Overall, the trial was consistent with the totality of clinical trial evidence, indicating that prognosis is improved when LDL cholesterol is driven into or near the physiologically normal level of <70 mg/dl.

## Is a Low-Density Lipoprotein Cholesterol Range of 30 to 70 mg/dl Feasible?

Several strategies are currently available to attain LDL cholesterol reductions of ≥50%. The most potent statins, simvastatin, atorvastatin, and rosuvastatin, are capable of producing reductions in LDL of 47%, 60%, and 63%, respectively, as monotherapy. Combination therapy can also substantially improve the lipid-lowering efficacy of statin therapy. Specifically, ezetimibe typically reduces LDL cholesterol an additional 25% when added to statin therapy.[19] Other options include niacin and plant sterols or stanol esters in combination with statin therapy. Although omega-3 oils do not reduce LDL cholesterol levels, they are effective alone and when added to statins for further reducing major CAD events by 19%, as shown by the Japan EPA Lipid Intervention Study presented by Dr. Yokoyama during the late-breaking clinical trials session at the American Heart Association Scientific Sessions in 2005.

## Percentage Low-Density Lipoprotein Cholesterol Reduction as a Treatment Strategy

Some experts have suggested that a specific LDL cholesterol threshold is somewhat arbitrary, and if clinically apparent atherosclerosis is noted, aggressive cholesterol reduction is warranted regardless of the absolute baseline LDL cholesterol level.[2] LDL cholesterol reductions of 50% in secondary prevention and 30% in primary prevention are supported by the cumulative randomized trial experience.[1] Our group analyzed major secondary prevention studies to explore the relation between percent LDL cholesterol reduction and CAD events (nonfatal myocardial infarction or cardiovascular death). We found a significant correlation ($p < 0.02$) between percent reduction in LDL cholesterol and relative risk reduction of CAD events, as demonstrated in Figure 2. This relation was present regardless of whether the therapy that produced the decrease in LDL cholesterol was a partial ileal bypass operation or any of a variety of statins.

Recently, a prospective meta-analysis of data from 90,056 patients in 14 randomized trials of statins showed a highly significant and linear relation between LDL reduction and overall survival.[20] This study reported that for every 1 mmol/L (39 mg/dl) reduction in LDL cholesterol over a 5-year period, all-cause mortality was reduced 12% ($p < 0.0001$). For example, a 76 mg/dl LDL cholesterol reduction from 146 to 70 mg/dl (a 52% decrease) would be expected to reduce all-cause mortality by 24% over a 5-year period, and a LDL cholesterol reduction from 184 to 70 mg/dl (a 62% decrease) would reduce all-cause mortality by 36%. The magnitude of LDL cholesterol reduction, but not the specific lipid therapy used, determined the degree of benefit. These findings suggest that pleiotropic effects of statins, if present, accrue in proportion to the degree to which LDL cholesterol is reduced, not some "magical" effect of a specific agent. The recent Fenofibrate Intervention and Event Lowering in Diabetes study also demonstrated the over-riding importance of LDL cholesterol reduction for improving CAD prognosis.[21] In this study, involving 9,795 patients, fenofibrate reduced LDL cholesterol by 12% and triglycerides by 30% but did not significantly reduce either CAD death or all-cause mortality.

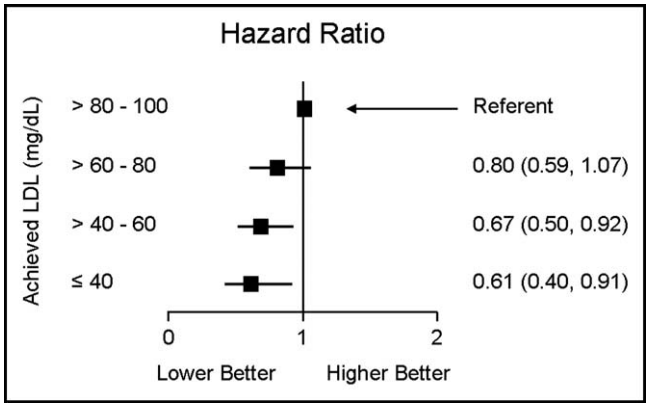


Figure 3. More aggressive LDL cholesterol reduction in the Pravastatin or Atorvastatin Evaluation and Infection Therapy study was not only safe but also associated with improved outcomes.[7]

## Safety of Aggressive Low-Density Lipoprotein Reduction

Recent data indicate that subjects with naturally low LDL cholesterol levels or those treated with statin therapy have improved longevity.[22] A recent analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy study[7] showed that LDL cholesterol reduction to very low levels (<40 mg/dl) was not only safe but also more effective at preventing adverse events than less aggressive reductions (Figure 3). The cumulative body of randomized data shows no effect of statins on the incidence of cancer.[23]

The principal safety concerns with statin therapy involve myalgia or myopathy and hepatotoxicity. The incidence of statin-associated muscle pain and weakness is estimated to be 1% to 5%. Severe myopathy with rhabdomyolysis occurs in about 1 to 3 patients per 10,000 treated, with little difference among the marketed statins.[23,24] When rhabdomyolysis does occur, it usually is in the context of predisposing risk factors such as diabetes, major surgery, hypothyroidism, liver failure, or renal failure. Deaths due to statin-related rhabdomyolysis are very rare (about 1 in every 10 million treated patients).[24]

Although the risks for myopathy and abnormal liver function tests are dose dependent for each statin, the greater reductions in LDL cholesterol seen with the more potent statins do not appear to carry a greater risk for toxicity than do more moderate LDL cholesterol reductions.[25]

## Other Beneficial Effects of Aggressive Low-Density Lipoprotein Cholesterol Reduction

Although speculative, it may be that elevated LDL cholesterol over a lifetime can predispose to a wide variety of chronic "age-related" degenerative diseases commonly seen in modern civilization. If the physiologically normal LDL cholesterol range is, as we believe, 30 to 70 mg/dl, it is possible that lowering elevated LDL cholesterol levels to levels closer to this truly normal range may improve not just atherosclerosis and its complications but also other diseases commonly attributed to the aging process. Statins have been reported to reduce the incidence of symptomatic peripheral vascular disease,[26] dementia,[27] and, in observational studies, macular degeneration[28] and fractures due to osteoporosis.[29] Confirmation of these potential unintended benefits of statin therapy awaits prospective trials, some of which are currently under way.

1. O'Keefe JH Jr, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. *J Am Coll Cardiol* 2004;43:2142–2146.
2. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ* 2002;324:1570–1576.
3. Grundy SM, Cleeman JI, Bairey Merz CN, Brewer HB, Hunninghake DB, Pasternak RC, Smith SC. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *J Am Coll Cardiol* 2004;44:720–732.
4. Davidson M, Maron D, Fonarow G, Maki K, Pearson T, Dicklin M. Implications of the new recommendations from the National Cholesterol Education Program Writing Group: results from a national survey of lipid management. *J Am Coll Cardiol* 2005;45:128.
5. Cordain L, Eaton SB, Miller JB, Mann N, Hill K. The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic. *Eur J Clin Nutr* 2002;56(suppl):S42–S52.
6. Cohen M. The significance of long-term changes in human diet and food economy. In: Harris M, Ross EB, eds. Food and Evolution: Toward a Theory of Human Food Habits. Philadelphia, PA: Temple University Press, 1987:261–283.
7. Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. *J Am Coll Cardiol* 2005;46:1411–1416.
8. Buchwald H, Varco RL, Matts JP, Long JM, Fitch LL, Campbell GS, Pearce MB, Yellin AE, Edmiston WA, Smink RD Jr, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). *N Engl J Med* 1990;323:946–955.
9. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;257:3233–3240.
10. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001; 357:577–581.
11. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 2002;106:2055–2060.
12. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis. The ASTEROID Trial. *JAMA* 2006;295:1556–1565.
13. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344:1959–1965.
14. Feldman T, Frazier N, Shah A, Maccubbin D, Tribble D, Donahue S. Efficacy and safety of ezetimibe/simvastatin in elderly patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2005;45:392A.

15. Stein EA, Schleman M, Harris S, Sager P. Further reduction of low-density lipoprotein cholesterol and C-reactive protein with the addition of ezetimibe to maximum-dose rosuvastatin in patients with sever hypercholesterolemia. *J Am Coll Cardiol* 2005;45:392A.
16. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504.
17. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425–1435.
18. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, Tsai J. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;294:2437–2445.
19. Masana L, Mata P, Gagne C, Sirah W, Cho M, Johnson-Levonas AO, Meehan A, Troxell JK, Gumbiner B. Long-term safety and tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: a multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. *Clin Ther* 2005; 27:174–184.
20. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–1278.
21. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–1861.
22. O'Keefe JH Jr, Cordain L. Cardiovascular disease resulting from a diet and lifestyle at odds with our Paleolithic genome: how to become a 21st-century hunter-gatherer. *Mayo Clin Proc* 2004;79:101–108.
23. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk, a meta-analysis. *JAMA* 2006;295:74–80.
24. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681–1690.
25. Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. *Am Heart J* 2005; 149:464–473.
26. Mohler ER III, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003;108:1481–1486.
27. Etminan M, Gill S, Samii A. The role of lipid-lowering drugs in cognitive function: a meta-analysis of observational studies. *Pharmacotherapy* 2003;23:726–730.
28. McGwin G Jr, Owsley C, Curcio CA, Crain RJ. The association between statin use and age related maculopathy. *Br J Ophthalmol* 2003;87:1121–1125.
29. Bauer DC, Mundy GR, Jamal SA, Black DM, Cauley JA, Ensrud KE, van der Klift M, Pols HA. Use of statins and fracture: results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials. *Arch Intern Med* 2004;164:146–152.