

HMG CoA Reduction in Patients with Average Cholesterol Concentrations

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Featured Article: Sacks FM, Pfeffer MA, Moyer LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–9.⁴

In 1984, a National Heart, Lung and Blood Institute trial demonstrated that reducing LDL cholesterol (LDL-C)⁵ with a combination of diet and large doses of the cholesterol-binding resin cholestyramine reduced coronary events (1) and slowed the progression of coronary artery obstruction (2) in men with increased cholesterol concentrations. Resins were not well tolerated, however, and patient compliance was poor. Subsequently, the availability of 3-hydroxy-3-methylglutaryl-coenzyme A (HmG CoA) reductase inhibitors changed the approach to cholesterol management, because these drugs were well tolerated and caused marked reductions in total cholesterol (TC) and LDL-C in the majority of individuals.

Two important clinical-outcome trials were launched promptly for patients with hypercholesterolemia. The Scandinavian Simvastatin Survival Study (3) enrolled patients with coronary artery disease and hypercholesterolemia [average TC, 261 mg/dL (6.6 mmol/L); average LDL-C, 188 mg/dL (4.87 mmol/L)], and the West of Scotland Coronary Prevention Study (4) used pravastatin in men without clinical coronary disease [average TC, 272 mg/dL (7.0 mmol/L); average LDL-C, 192 mg/dL (5.0 mmol/L)].

On the basis of the earlier findings (1, 2), we assumed that these trials would show clinical benefit; however, patients with the high concentrations of cir-

culating TC and LDL-C in these trials constituted only a minority of the patients with coronary artery disease. It was not clear whether reducing TC and LDL-C in patients with established coronary artery disease but with concentrations similar to those in the general population would also produce clinical benefit. We focused our attention on this group because a majority of patients with coronary artery disease have TC and LDL-C concentrations that are similar to those in the general population.

While the Scandinavian Simvastatin Survival Study and the West of Scotland Coronary Prevention Study were still early in their recruitment phase, we developed the Cholesterol and Recurrent Events (CARE) trial, an investigator-initiated, randomized clinical trial supported by Squibb (now Bristol-Myers Squibb). Between 1989 and 1991, we enrolled 4159 patients who had experienced a myocardial infarction with an average TC concentration of 209 mg/dL (5.4 mmol/L) and an average LDL-C of 139 mg/dL (3.6 mmol/L) (concentrations similar to those of the adult population in the US at the time) to receive placebo or 40 mg pravastatin daily. After 5 years, we found that the frequency of occurrence of the primary end point (fatal coronary event or nonfatal myocardial infarction) was reduced significantly, by 24%, from 13.2% in the placebo-treated patients to 10.2% ($P = 0.003$). The frequency of stroke was also reduced significantly (31%) (5), as was the need for coronary revascularization (27%). Benefit was observed in important subgroups: diabetics, older patients (>65 years) (6), women, patients with left ventricular dysfunction, and those whose TC, LDL-C, and HDL-C values were above or below the median values.

The report providing results of the CARE trial has been cited frequently and has contributed importantly to a change in the guidelines for cholesterol management (7). Consequently, the trial expanded greatly the number of coronary artery disease patients with TC and LDL-C concentrations similar to those in the general population who were treated with HmG CoA reductase inhibitors.

We made 3 additional interesting observations in the CARE trial: (a) The concentration of an inflammatory biomarker, C-reactive protein (CRP), was higher in the patients who developed a primary end point than in those who did not (8); (b) the magnitude of the risk

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⁴ This article has been cited more than 4150 times since publication.

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Received March 23, 2011; accepted April 12, 2011.

Previously published online at DOI: 10.1373/clinchem.2011.164038

⁵ Nonstandard abbreviations: LDL-C, LDL cholesterol; HmG CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; TC, total cholesterol; CARE, Cholesterol and Recurrent Events (trial); CRP, C-reactive protein; JUPITER, Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (trial); PROVE-IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (trial).

reduction associated with pravastatin was significantly greater among patients with increased CRP concentrations (8); and (c) pravastatin significantly reduced CRP, independently of the change in LDL-C (9). These observations provided the first evidence that statins were more effective among patients with underlying vascular inflammation and that they might have clinically relevant antiinflammatory actions. These observations from the CARE trial provided much of the basis for the JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, which demonstrated that statin therapy is highly effective in the primary prevention of cardiovascular events among individuals with increased CRP (>2 mg/L), even when LDL-C concentrations are in the low-to-normal range [<130 mg/dL (<3.37 mmol/L)] (10).

Since the publication of the CARE trial results, the average concentrations of TC and LDL-C have declined, both in the general population and in patients with coronary artery disease. In patients who had experienced an acute coronary event, in a trial called PROVE-IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22), we observed that more-intensive lowering of the LDL-C concentration with a high dose of a very potent HmG CoA reductase inhibitor (80 mg/day atorvastatin) to an average LDL-C of 62 mg/dL (1.6 mmol/L) led to significantly better clinical outcomes than those achieved by 40 mg pravastatin daily [95 mg/dL (2.5 mmol/L)], the regimen that had been found in the CARE trial to be superior to placebo (11). That result led to the conclusion of “the lower the better” for LDL-C after an acute coronary event.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.

Consultant or Advisory Role: M.A. Pfeffer, Affectis, Anthera, Boehringer, Boston Scientific, Bristol-Myers Squibb, GlaxoSmith-

Kline, Medtronic, Novartis, Roche, Sanofi-aventis, Servier, and University of Oxford; P.M. Ridker, Genzyme, Boehringer, and Vascular Biogenics.

Stock Ownership: None declared.

Honoraria: None declared.

Research Funding: E. Braunwald, AstraZeneca, Bristol-Myers Squibb, and Merck; M.A. Pfeffer, Amgen, Baxter, Celladon, Novartis, and Sanofi-aventis; P.M. Ridker, AstraZeneca, Novartis, Sanofi-aventis, and Amgen.

Expert Testimony: F.M. Sacks, Abbott.

Other remuneration: M.A. Pfeffer, Novartis and Boehringer; P.M. Ridker, co-inventor on patents held by the Brigham and Women's Hospital relating to the use of inflammatory markers in cardiovascular disease that have been licensed to AstraZeneca and Siemens.

References

1. Lipid Research Clinic Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351–64.
2. Brensike JF, Levy RI, Kelsey SF, Passamani ER, Richardson JM, Loh IK, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. *Circulation* 1984;69:313–24.
3. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–9.
4. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al., for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–7.
5. Plehn JF, Davis BR, Sacks FM, Rouleau JL, Pfeffer MA, Bernstein V, et al. Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol and Recurrent Events (CARE) study. The CARE Investigators. *Circulation* 1999;99:216–23.
6. Lewis SJ, Moye LA, Sacks FM, Johnstone DE, Timmis G, Mitchell J, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med* 1998;129:681–9.
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–97.
8. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, et al., for the Cholesterol and Recurrent Events (CARE) Investigators. Inflammation, pravastatin and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation* 1998;98:839–44.
9. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E, for the Cholesterol and Recurrent Events (CARE) Investigators. Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation* 1999;100:230–5.
10. Ridker PM, Sanielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–207.
11. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–504.