# The Prove It Study: Is It Really a Landmark Study or Another Piece of a Very Important Puzzle?

Reviewed by Henry N. Ginsberg, MD

## STUDY

Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 350:1495–1504, 2004

## SUMMARY

**Design.** This was a randomized, blinded, double placebo–controlled, comparison of pravastatin, 40 mg daily, versus atorvastatin, 80 mg daily, in patients who presented to hospitals with an acute coronary syndrome (ACS). The goal of the study was to determine if "standard" therapy to lower LDL cholesterol levels to the recommended goal of about 100 mg/dl with 40 mg pravastatin was as effective in preventing further coronary events as more aggressive therapy that lowered LDL cholesterol levels to about 70 mg/dl with 80 mg atorvastatin. ACS was defined as an acute myocardial infarction (MI) or high-risk unstable angina.

**Subjects.** The study enrolled 4,162 adults with an average age of 58 years. Twenty-two percent of the subjects were female, and 90% were white. Eighteen percent had diabetes, 18% had had a previous MI, and 11% had undergone previous coronary bypass surgery. One-third presented with high-risk unstable angina and the rest with an acute MI (with or without ST elevation). Sixty-nine percent had a percutaneous transluminal coronary angioplasty (PTCA) procedure during their hospitalization.

The baseline median LDL cholesterol level, obtained either within 24 hours of admission or within the previous 6 months, was 106 mg/dl, and 25% of the subjects were on statin treatment at the time of admission. The median baseline HDL cholesterol level was 38 mg/dl, and the median baseline triglyceride level was 155 mg/dl.

**Methods.** Patients were randomized within 10 days of their event to either pravastatin or atorvastatin and otherwise treated according to standards of care. Regularly scheduled follow-up visits occurred over 18–36 months, with a mean follow-up of 24 months. The study was stopped after 925 events had been reported.

The study was designed as a noninferiority trial, with the hypothesis being that more aggressive LDL cholesterol lowering below the recommended guidelines would have no further benefit on events. The primary endpoints during follow-up were death from any cause, MI, documented unstable angina requiring hospitalization, PTCA or coronary bypass surgery, or stroke.

**Results.** The median LDL cholesterol during follow-up was 95 mg/dl in the pravastatin group and 62 mg/dl in the atorvastatin group. HDL cholesterol levels rose 8.1 and 6.5% in the two groups, respectively. Changes in triglycerides were not reported. C-reactive protein fell from 12.3 mg/l at baseline (in the acute event stage) to 2.1 mg/l with pravastatin and 1.3 mg/l with atorvastatin.

The rate of primary endpoints was 26.3% in the pravastatin group and 22.4% in the atorvastatin group. This was equal to a 16% reduction in the hazards ratio (risk of having an event during the trial) in the atorvastatin group. The most prevalent single event was revascularization, which was lower by 14% in the atorvastatin group.

**Conclusions.** Among patients with a recent ACS event, more aggressive lipid-lowering therapy, with goals significantly below those proposed by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines can provide additional benefit.

## COMMENTARY

This study illustrates the fact that there are many ways to view results of trials and potentially many ways to extrapolate their results to clinical practice. But first, it is important to review the underlying hypothesis behind the design of Prove It.

The Cholesterol and Recurring Events (CARE) trial,[1] which was a secondary prevention study, found no apparent benefit of LDL lowering with 40 mg pravastatin for individuals whose baseline LDL cholesterol levels were < 125 mg/dl or in whom LDL cholesterol was lowered to < 125 mg/dl during the trial. Those results provided the sponsor of CARE, Bristol-Myers Squibb, with the rationale for the Prove It study. On the other hand, several other studies, including the Scandinavian Simvastatin Survival Study and the Post Coronary Artery Bypass Graft studies, indicated that more lowering of LDL

cholesterol to lower absolute levels was associated with greater benefit than less LDL cholesterol lowering.[2] Indeed, in the Pravastatin Pooling Project, which included CARE, the West of Scotland Coronary Prevention Study, and the larger Long-Term Intervention With Pravastatin in Ischemic Disease trial, analysis of outcomes according to baseline LDL cholesterol levels did not show loss of efficacy of LDL lowering in the group with low baseline LDL cholesterol.[3] Additionally, in the Heart Protection Study (HPS), 30% reductions in LDL cholesterol were associated with ~ 25% reductions in cardiovascular events in patients with baseline LDL cholesterol < 100 mg/dl, 100–129 mg/dl, and > 129 mg/dl.[4] So overall, despite the initial observation in CARE, data from most of the other major trials indicated that greater lowering of LDL cholesterol, or lowering of LDL cholesterol to lower concentrations, was better than modest lowering and/or modest goals. In particular, the results of the HPS suggested strongly that Prove It would show an advantage for the atorvastatin treatment group.

So, does Prove It provide us with any new and unique data that could change our way of treating people? Many experts in the field would say "no." Earlier summary analyses of the major cholesterol-lowering trials have shown that *1*) the degree of lowering is linearly related to the reduction in events, and *2*) the LDL cholesterol concentration achieved during the trial is linearly related to the absolute event rate. Thus, one would have expected that in Prove It, the much greater reduction in LDL cholesterol achieved with atorvastatin (from 106 to 62 mg/dl, or about 42%) would result in greater reductions in events compared to pravastatin treatment, which lowered LDL cholesterol much less (from 106 to 95 mg/dl, or about 11%). Indeed, Prove It is reminiscent of the ALLHAT Lipid Lowering Trial, a substudy within the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, in which treatment of 40 mg pravastatin did not significantly reduce coronary heart disease events (9%, not significant). In that study, the difference in LDL cholesterol between the pravastatin-treated group and the control group (in which there was about 20% open-label use of statins) was only 17%.[5]

On the other hand, Prove It did use a head-to-head design in a population where both groups could reach the ATP III recommended guidelines of an LDL cholesterol < 100 mg/dl. In that sense, it does give health care providers some additional guidance regarding the use of the recommended goals for LDL cholesterol. For example, the results of Prove It support the view that whatever the starting LDL cholesterol level is, particularly in previously untreated patients, the occurrence of a coronary event indicates that the level is not low enough and that further significant lowering will benefit the patient. In other words, aggressive combinations of risk factors (multiple risk factors, diabetes) and/or the existence of clinical atherosclerotic cardiovascular disease require aggressive lipid-altering therapy.

What remains unclear, at least to this reviewer, is whether there is a limit to the benefit one can obtain from LDL cholesterol lowering. Specifically, the trials to date have achieved, at most, 40–45% LDL lowering; this is clearly better than 10–20% lowering and probably better than 20–30% lowering. What is not clear, however, is whether 50 or 60 or 70% lowering will be significantly better than 40–45% lowering.

Additionally, none of these studies, including Prove It, gives us a magic number for LDL cholesterol. If you reduce a patient's LDL cholesterol from 200 to 100 mg/dl or from 120 to 60 mg/dl, you will probably get similar relative reductions in risk. Whether the patient at 60 mg/dl has lower absolute risk than the patient at 120 mg/dl will depend, therefore, on whether the two patients' absolute risks differed at baseline.

Maybe the most important take-home message from Prove It, as from most of the other large statin trials, is that significant reductions in LDL cholesterol, rather than any single number, should be the goal for patients at high risk of having coronary or other vascular events.

## REFERENCES

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