CME CREDIT

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LESSONS FROM THE PROVE-IT TRIAL

Higher dose of potent statin better for high-risk patients

ABSTRACT

The Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE-IT/TIMI-22) showed that in patients with acute coronary syndromes, aggressive lipid-lowering using atorvastatin 80 mg/day provided greater protection against death or major cardiovascular events than did moderate lipid-lowering using pravastatin 40 mg/day. Lowering the low-density lipoprotein cholesterol level to approximately 62 mg/dL with atorvastatin resulted in a 16% reduction in cardiovascular end points.

AGGRESSIVE LIPID-LOWERING with high-dose statin therapy should be instituted in patients with acute coronary syndromes, according to the results of the recent Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study,[1] published by the investigators of the Thrombolysis in Myocardial Infarction (TIMI) trials.

Compared with moderate-dose pravastatin therapy, high-dose atorvastatin was associated with a significantly lower incidence of the composite end point of death, myocardial infarction, unstable angina, revascularization, and stroke, as early as 30 days after therapy was started. This trial has prompted debate over the equivalence of different statin formulations and target levels of low-density lipoprotein cholesterol (LDL-C) for high-risk patients. It has also started debate over whether lipid-lowering guidelines need to be changed: ie, how low is too low?

Why PROVE-IT was needed, the study design, results, and clinical implications are the topics of this discussion.

BACKGROUND

Ever since lovastatin was introduced in 1987, statins have been deemed miracle drugs by many, due to their efficacy in reducing the incidence of cardiovascular death, heart attacks, and stroke. In fact, one editorial asserted that statins "are to atherosclerosis what penicillin was to infectious diseases."[2]

The PROVE-IT trial raised the question of whether current lipid-lowering guidelines are strict enough

Several major clinical trials published in the last decade have definitively demonstrated the beneficial effects of various statin drugs.

The first of these trials was the Scandinavian Simvastatin Survival Study (4S), a secondary prevention study published in 1994, which demonstrated that patients with coronary heart disease who were treated with simvastatin had significantly lower rates of mortality, major coronary events, and myocardial revascularization compared with patients receiving placebo.[3]

This study was followed closely by the West of Scotland Coronary Prevention Study Group (WOSCOPS) trial, a primary prevention trial that demonstrated that men with hypercholesterolemia who were treated with pravastatin had a lower incidence of myocardial infarction and death from cardiovascular causes compared with those taking placebo.[4]

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These results held true in the Air Force/Texas Coronary Atherosclerosis Prevention study (AFCAPS/TexCAPS), which demonstrated that, compared with placebo, lovastatin treatment was associated with a lower risk for a first major coronary event in men and women with no history of coronary artery disease and average cholesterol levels.[5]

The largest clinical trial to date evaluating statin therapy was the Heart Protection study (HPS), which enrolled 20,536 adults with coronary disease, other occlusive arterial disease, or diabetes. Patients received either simvastatin or placebo. As did prior studies, the HPS found significantly lower first event rates for nonfatal myocardial infarction or coronary death, nonfatal or fatal strokes, and for coronary revascularization with statin therapy compared with placebo. Surprisingly, however, this study showed an equivalent benefit in patients with a starting LDL-C level below 100 mg/dL, compared with those with high LDL-C levels.[6]

Similarly, the recently published Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA) study[7] also demonstrated significantly fewer cardiovascular end points in hypertensive, nondyslipidemic patients treated with a statin. In this prospective study, 10,305 patients with hypertension and at least three other cardiovascular risk factors, with a starting nonfasting total cholesterol level of 6.5 mmol/L (251 mg/dL) or less, were randomly assigned to atorvastatin 10 mg daily or placebo. The trial was terminated early, at 3.3 years, due to a 36% lower rate of death and nonfatal myocardial infarction in the atorvastatin group.[7]

In MIRACL and CARE, statins seemed to protect patients soon after myocardial infarction

UNANSWERED QUESTIONS: HOW LOW IS TOO LOW?

Do these studies render obsolete the recommendations of the National Cholesterol Education Program, which advocates a target LDL-C level of less than 100 mg/dL in patients with coronary artery disease or diabetes?[8] These results fueled debate about "How low is too low?" Should we pursue aggressive lowering of LDL-C levels beyond currently established guidelines? Is there a lower cutoff LDL-C level, below which further reductions may be harmful? The answers to these questions remain unknown and are a subject of great interest.

What epidemiologic studies show

Epidemiologic studies have previously identified a relationship between low serum levels of total cholesterol (< 130 mg/dL) and increased all-cause mortality. However, this association is confounded by concomitant illness, such as cancer, malnutrition, and liver disease. Two ongoing trials, the Treating to New Targets (TNT) study[9] and the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study,[10] aim to specifically address the question of whether lowering LDL-C levels below currently recommended guidelines yields incremental clinical benefit.

Additional intervention trials

In parallel with the aforementioned statin trials, investigations were being pursued in the setting of myocardial infarction. In the Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) study,[11] in which atorvastatin or placebo was given within 24 to 96 hours after an acute coronary syndrome, patients taking atorvastatin had significantly fewer recurrent ischemic events within the first 16 weeks of therapy.[11] The Cholesterol and Recurrent Events (CARE) trial,[12] which enrolled patients 3 to 20 months after myocardial infarction, demonstrated a significantly lower frequency of major cardiovascular end points among patients randomized to pravastatin, compared with placebo.[12]

Are all statins equal?

While clearly demonstrating the protective effects of statin therapy, these trials engendered even more questions. Is the benefit a class effect of statin therapy, or is there a difference in efficacy between various statin agents?

For instance, the initial statin studies generally used a fixed dose of 40 mg and generated similar results: they showed an average reduction of 25% to 35% in LDL-C levels in patients treated with a statin; these patients had an approximately 24% to 31% reduction in the risk of coronary heart disease, death, or myocardial infarction. However, atorvastatin,

introduced in 1997, has a more powerful lipid-lowering effect: it appears to be about 50% more powerful than simvastatin in their respective maximal doses. In an atorvastatin titration study, 40 mg/day reduced LDL-C to less than 100 mg/dL in 64% of patients, and 80 mg/day reduced LDL-C to less than 100 mg/dL in 82% of patients.[13] However, the relationship between cholesterol-lowering and cardiovascular risk remains incompletely defined; it is unclear, at lower cholesterol levels, whether further reductions confer additional protection.

How low should we go with LDL-C?

Several studies using surrogate cardiovascular end points aimed to address this question. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) study, published in 2002,[14] compared the effect of aggressive lipid-lowering with atorvastatin 80 mg/day with a moderate lipid-lowering strategy of pravastatin 40 mg/day on carotid intima medial thickness. As anticipated, atorvastatin had a substantially more potent effect on LDL-C reduction than pravastatin. Interestingly, atorvastatin induced progressive regression of medial thickness over 12 months, whereas the thickness was stable in the pravastatin group.

Similarly, the Dutch ASAP study (of the effect of aggressive vs conventional lipid-lowering on atherosclerosis progression in familial hypercholesterolemia) compared atorvastatin 80 mg/day with simvastatin 40 mg/day in patients with familial hypercholesterolemia, and also demonstrated a unique regression of carotid intima medial thickness in the atorvastatin group.[15]

The recently published Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL) trial[16] used the same regimen of atorvastatin vs pravastatin, with the end point of coronary artery atheroma burden, as measured by intravascular ultrasound. This study demonstrated that patients treated with high-dose atorvastatin had no change in atheroma burden over 18 months of therapy, whereas patients treated with pravastatin showed progression of coronary atherosclerosis.[16]

Benefit of more intensive lipid-lowering

These studies implied that more intensive lipid-lowering therapy is the preferred approach, and that statins may have multiple beneficial effects besides lipid-lowering.

For instance, the REVERSAL trial demonstrated a 36.4% decrease in C-reactive protein levels in the atorvastatin group, compared with a 5.2% decrease in the pravastatin group, lending further support to the theory that statins may also have beneficial anti-inflammatory effects.

AIMS OF THE PROVE-IT TRIAL

The PROVE-IT trial addressed the question of whether aggressive lipid-lowering reduces the number of end-point events compared with moderate lipid-lowering.

The primary aim of the study was to determine if standard therapy to lower LDL-C (pravastatin 40 mg/day) provides a clinical benefit similar to atorvastatin 80 mg/day, which markedly lowers LDL-C. It was hypothesized that these two strategies would have equivalent clinical benefit in patients with acute coronary syndromes treated for an average of 2 years.

The secondary aim was to examine the role of *Chlamydia pneumoniae* infection in cardiovascular disease by evaluating the effectiveness of the antibiotic gatifloxacin in reducing cardiovascular events. The results of the gatifloxacin arm of the study have not yet been published.

The study was sponsored by Bristol-Myers Squibb, the manufacturer of pravastatin.

REVERSAL trial data support a beneficial anti-inflammatory effect of statins

DESIGN OF THE PROVE-IT TRIAL

The PROVE-IT trial was a randomized, double-blind, head-to-head comparison. It was designed as a time-to-event trial and was terminated after a prespecified number of events had occurred. In all, 4,162 patients were enrolled at 349 sites in eight countries.

TABLE 1 lists the inclusion and exclusion criteria. All patients were hospitalized for an acute coronary syndrome, either acute myocardial infarction with or without ST-segment elevation, or positive serum levels for myocardial enzymes, within the preceding 10 days.

TABLE 1

Inclusion and exclusion criteria in the PROVE-IT trial

Inclusion criteria

- 18 years of age or older
- Acute coronary syndrome (myocardial infarction or high-risk unstable angina) within the preceding 10 days
- Completion of any planned percutaneous interventions
- Total cholesterol ≤ 240 mg/dL if not previously on lipid-lowering therapy (measured within the first 24 hours of acute coronary syndrome or within the 6 months prior)
- Total cholesterol ≤ 200 mg/dL if previously on lipid-lowering therapy

Exclusion criteria

- Life expectancy < 2 years
- Receiving any statin at a dose of 80 mg/day
- Receiving fibric acid derivative or niacin which could not be discontinued before randomization
- Received CYP-450 3A4-inhibiting drugs (eg, ketoconazole, clarithromycin, erythromycin, ritonavir) within 1 month prior to randomization, or likely to require such treatment
- Percutaneous coronary intervention within the prior 6 months (other than for the qualifying events), coronary artery bypass surgery within the previous 2 months, or scheduled to undergo bypass surgery in response to the index event
- Prolonged QT interval
- Obstructive hepatobiliary or other serious liver disease
- Elevation in creatine kinase level to greater than three times the upper limit of normal (except patients with creatine kinase elevations due to acute myocardial infarction)
- Creatinine > 2.0 mg/dL

All patients received the standard medical and interventional treatments for acute coronary syndromes and were randomized to receive either pravastatin 40 mg/day or atorvastatin 80 mg/day in a double-blind fashion. They were seen for follow-up visits and dietary counseling at 30 days, at 4 months, and every 4 months thereafter until the termination of the study. Cholesterol levels were checked periodically, and the dose of pravastatin was increased from 40 mg/day to 80 mg/day if the LDL-C concentration exceeded 125 mg/dL on two consecutive visits. The patients were followed for an average of 24 months, and the trial was terminated when 925 events had been reported.

End points

The primary end point of the PROVE-IT trial was a composite of death from any cause, myocardial infarction, unstable angina requiring rehospitalization, revascularization via percutaneous intervention or bypass surgery more than 30 days after the index event, and stroke.

Secondary end points were the risk of death from coronary heart disease, nonfatal myocardial infarction, revascularization, risk of death from coronary heart disease or nonfatal myocardial infarction, and the risk of the individual components of the primary end point.

PROVE-IT RESULTS

Cholesterol-lowering effect

The baseline LDL-C concentration was 106 mg/dL in both groups—a low level that reflects the fact that 25% of patients enrolled were already receiving statin therapy. After 2 years of treatment, the median LDL-C concentration had declined to 62 mg/dL in the atorvastatin group and to 95 mg/dL in the pravastatin group. The difference became apparent very early, within the first 30 days of therapy, and was consistent over time (FIGURE 1).[1]

Compared with baseline LDL-C levels, at 30 days the median LDL-C level in patients not previously treated with a statin had declined by 51% in the atorvastatin group and by 22% in the pravastatin group. Among patients previously treated with a statin, LDL-C levels declined by 32% in the atorvastatin group vs no change in the pravastatin group.

Clinical outcomes

In an intention-to-treat analysis, the Kaplan-Meier event rates of the primary end point at 2 years were 22.4% in the atorvastatin group and 26.3% in the pravastatin group, a 16% reduction in relative risk in the group receiving aggressive therapy (P = .005; FIGURE 2).[1] The individual components of the primary end point showed a consistent benefit favoring atorvastatin, except for stroke, likely due to a low event rate.

The relative risk reductions for the individual end points with aggressive therapy were as follows:

- Need for revascularization—14% reduction (P = .04)
- Recurrent unstable angina—29% reduction (P = .02)
- Death from any cause—28% reduction (P = .07)
- Death or myocardial infarction—18% reduction (P = .06).

The atorvastatin group also had significantly lower rates of the composite secondary end points, as follows:

- Death due to coronary heart disease, myocardial infarction, or revascularization—14% reduction (P = .029)
- Death, myocardial infarction, or urgent revascularization—25% reduction (P < .001). Of note, this end point was reported on post hoc analysis and was not a prespecified secondary end point.

In subgroup analyses, the benefit of atorvastatin was consistent across all groups analyzed, including men and women, patients with unstable angina and myocardial infarction, and those with and without diabetes.

CLINICAL IMPLICATIONS OF PROVE-IT

The results of the PROVE-IT trial came as a surprise, as the trial was designed to demonstrate that pravastatin was not inferior to atorvastatin. Instead of being equivalent to moderate lipid-lowering therapy, high-dose atorvastatin demonstrated a consistent, dramatic lowering of LDL-C and reduction in clinically important end points.

While prior placebo-controlled studies such as the HPS[6] showed a difference in event rates after approximately 18 months of statin

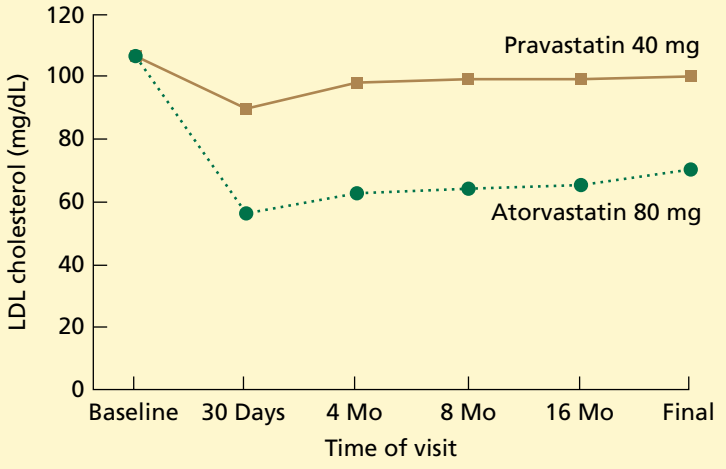

FIGURE 1. Median low-density lipoprotein (LDL) cholesterol levels during the study.

FROM CANNON CP, BRAUNWALD E, MCCABE CH, ET AL. INTENSIVE VERSUS MODERATE LIPID LOWERING WITH STATINS AFTER ACUTE CORONARY SYNDROMES. N ENGL J MED 2004; 350:1495–1504. REPRINTED BY PERMISSION OF THE NEW ENGLAND JOURNAL OF MEDICINE.

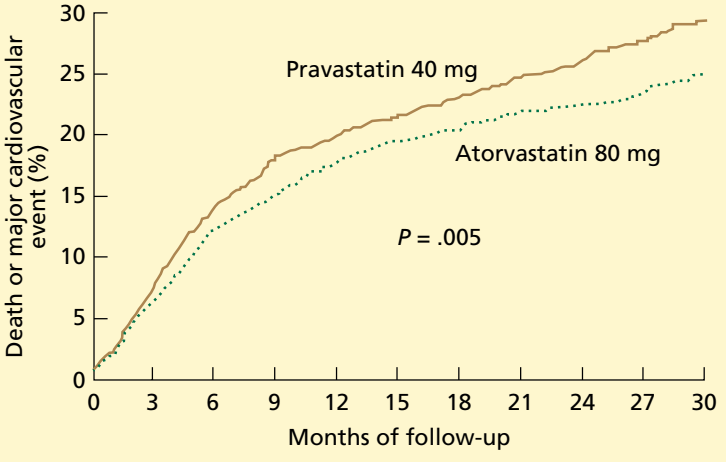

FIGURE 2. Kaplan-Meier estimates of the incidence of the primary end point of death from any cause or a major cardiovascular event. Intensive lipid-lowering with the 80-mg dose of atorvastatin, as compared with moderate lipid-lowering with the 40-mg dose of pravastatin, reduced the hazard ratio for death or a major cardiovascular event by 16%.

FROM CANNON CP, BRAUNWALD E, MCCABE CH, ET AL. INTENSIVE VERSUS MODERATE LIPID LOWERING WITH STATINS AFTER ACUTE CORONARY SYNDROMES. N ENGL J MED 2004; 350:1495–1504. REPRINTED BY PERMISSION OF THE NEW ENGLAND JOURNAL OF MEDICINE.

therapy, PROVE-IT demonstrated an early reduction, albeit not statistically significant, within the first 30 days. We know that recurrent cardiac events occur most commonly within the first month of an acute coronary syndrome.[17] Previous studies have shown that patients with acute myocardial infarction may harbor multiple complex coronary plaques.[17] Perhaps by stabilizing these plaques and providing rapid cholesterol-lowering, high-dose statin therapy may prevent subsequent plaque rupture.

The results of PROVE-IT do not stand alone. The National Heart, Lung, and Blood Institute's Post-Coronary Artery Bypass Graft (Post-CABG) trial,[18] published in 1999, showed that aggressive lipid-lowering to a target LDL-C concentration lower than 100 mg/dL (in this case with the relatively less-potent statin drug lovastatin, and cholestyramine when necessary) delays the progression of atherosclerosis in saphenous vein grafts.[18] Similarly, the recent REVERSAL trial[16] provides additional evidence of the benefits of more aggressive lipid-lowering therapy.

The cost may be untenable for those already on multiple drugs

These findings have profound clinical implications. In the United States alone, 36 million people meet the criteria for statin therapy.[19] The results of this study indicate that early and aggressive initiation of lipid-lowering medications in all eligible patients would result in a dramatic decline in the incidence of unstable angina, myocardial infarction, death from cardiovascular causes, and the need for revascularization. Not only would we be able to prevent initial heart attacks, we would be able to dramatically reduce the risk of future events in patients with established coronary heart disease. These results are on a par with the mortality reduction seen in patients with acute myocardial infarction treated with aspirin plus beta-blockers, which is now accepted as the standard of care.

OTHER CONSIDERATIONS

But before we all jump on the bandwagon of high-dose statin therapy, we should heed several words of caution.

Statins are costly

First and foremost is the issue of cost. Treatment with atorvastatin 80 mg/day costs approximately $1,200 per year. For senior citizens and others without prescription drug coverage, this expense will be largely out-of-pocket. Statins already account for the largest prescription drug expenditure nationwide.

Can our health care system afford this additional cost? For many Americans who are already taking necessary drugs for hypertension, congestive heart failure, diabetes, and other comorbidities, this cost may be untenable.

As physicians, we must be prepared to answer questions about which medications are absolutely necessary and which ones patients can live without. A reasonable approach to this problem lies in assessing the patient's risks. Those with high-risk features, such as diabetes and peripheral vascular disease, may gain the most from primary prevention with aggressive lipid-lowering therapy. In addition, PROVE-IT demonstrates that patients with recent myocardial infarction are at very high risk and are ideal candidates for secondary prevention. In this manner, high-dose statin therapy can be targeted towards patients with the highest event rates, while minimizing less cost-effective treatments for low-risk patients.

Statins have side effects

As expected, higher doses of atorvastatin resulted in a higher incidence of side effects. For example, 3.3% of patients treated with atorvastatin experienced a transaminase elevation to greater than three times the upper limit of normal, compared with 1.1% of patients in the pravastatin group. Similarly, 3.3% of patients taking atorvastatin had to stop the study medication due to myalgias or an elevation in creatine kinase levels.

We must bear these risks in mind when prescribing high-dose statins. We should carefully monitor patients for symptoms. These drugs may be contraindicated in patients with preexisting hepatic dysfunction.

Class effect or unique drug effect?

As with most well-designed studies, PROVE-IT raises several intriguing questions that will likely fuel further research. First is the issue of whether the results indicate a "class effect": Is the morbidity and mortality benefit seen in

the atorvastatin group due to the unique formulation of atorvastatin, or will equally potent statin regimens exert the same effect?

Do statins do more than lower lipids?

Secondly, is the benefit gained from statin therapy due solely to the lowering of LDL-C levels, or are there other biological mechanisms that are equally important?

The PROVE-IT trial showed a fall in C-reactive protein from equivalent baseline levels in each group to 2.3 mg/L in the pravastatin group and 1.3 mg/L in the atorvastatin group ($P < .001$).

Prior investigations have already proposed several mechanisms for the pleiotropic effects of statins. Statins appear to bind to the lymphocyte function-associated antigen-1 (LFA-1) site on leukocytes, thereby exerting potent anti-inflammatory effects. Statins also improve endothelial function in animal models of hypercholesterolemia by increasing the production of nitric oxide, a vasodilator, and decreasing the production of endothelin-1, a potent vasoconstrictor. Atorvastatin has also been shown to increase the number and the activity of circulating endothelial progenitor cells in patients with stable coronary heart disease, which may promote the growth of collateral circulation.[20]

With these and other data demonstrating the many biological effects of statins, our current dosing practices based on LDL-C levels may be misguided. Perhaps we should simply prescribe statins on the basis of target drug *dosages* that have demonstrated efficacy in clinical trials, such as atorvastatin 80 mg daily, rather than targeting a particular LDL-C level.

TAKE-HOME MESSAGES

PROVE-IT is a head-to-head trial demonstrating the superiority of one therapeutic approach (intensive lipid-lowering) over another (usual care), despite the initial study goal of demonstrating equivalence.

In addition, the PROVE-IT investigators convincingly demonstrated that aggressive statin therapy reduces recurrent ischemic events in patients with acute coronary syndromes. This trial confirms the results of earlier studies such as MIRACL,[11] which demonstrated the importance of starting statins in the setting of acute coronary syndromes, and subsequent observational and smaller randomized studies showing the benefit of prescribing lipid-lowering therapy within days of an acute coronary event.[21,22] By demonstrating significant benefit in patients at high risk, the PROVE-IT trial provides strong support for aggressive and early initiation of statins after an acute coronary syndrome to achieve a low LDL-C target of 60 to 70 mg/dL.

The results of PROVE-IT may conflict with the goal LDL-C levels set forth in the current National Cholesterol Education Program guidelines. This and other recent publications demonstrating the benefit of aggressive lipid-lowering therapy will prompt debate and perhaps a revision of the current guidelines.

Perhaps we should aim for target statin doses, not LDL-C levels

REFERENCES

1. **Cannon CP, Braunwald E, McCabe CH, et al.** Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350:1495–1504.
2. **Roberts WC.** The underused miracle drugs: the statin drugs are to atherosclerosis what penicillin was to infectious disease. Am J Cardiol 1996; 78:377–378.
3. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344:1383–1389.
4. **Shepherd J, Cobbe SM, Ford I, et al.** Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333:1301–1307.
5. **Downs JR, Clearfield M, Weis S, et al.** Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279:1615–1622.
6. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7–22.
7. **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.
8. 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) final report. Circulation 2002; 106:3143–3421.
9. **Waters DD, Guyton JR, Herrington DM, McGowan MP, Wenger NK, Shear C.** Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? Am J Cardiol 2004; 93:154–158.
10. **Crespin SR.** What does the future hold for diabetic dyslipidaemia? Acta Diabetol 2001; 38(Suppl 1):S21–S26.
11. **Schwartz GG, Olsson AG, Ezekowitz MD, et al.** Effects of atorva-

statin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001; 285:1711–1718.
12. **Sacks FM, Pfeffer MA, Moye LA, et al.** The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996; 335:1001–1009.
13. **Davidson MH, Nawrocki JW, Weiss SR, et al.** Effectiveness of atorvastatin for reducing low-density lipoprotein cholesterol to National Cholesterol Education Program treatment goals. Am J Cardiol 1997; 80:347–348.
14. **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.
15. **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.
16. **Nissen SE, Tuzcu EM, Schoenhagen P, et al.** Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291:1071–1080.
17. **Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW.** Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000; 343:915–922.
18. **Campeau L, Hunninghake DB, Knatterud GL, et al.** Aggressive cholesterol lowering delays saphenous vein graft atherosclerosis in women, the elderly, and patients with associated risk factors. NHLBI post coronary artery bypass graft clinical trial. Post CABG Trial Investigators. Circulation 1999; 99:3241–3247.
19. **Topol EJ.** Intensive statin therapy—a sea change in cardiovscular prevention. N Engl J Med 2004; 350:1562–1564.
20. **Bonetti PO, Lerman LO, Napoli C, Lerman A.** Statin effects beyond lipid lowering—are they clinically relevant? Eur Heart J 2003; 24:225–248.
21. **Aronow HD, Topol EJ, Roe MT, et al.** Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: an observational study. Lancet 2001; 357:1063-1068.
22. **Arntz HR, Agrawal R, Wunderlich W, et al.** Beneficial effects of pravastatin (+/-colestyramine/niacin) initiated immediately after a coronary event (the randomized Lipid-Coronary Artery Disease [L-CAD] Study). Am J Cardiol 2000; 86:1293–1298.

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CME ANSWERS

Answers to the credit test on page 679 of this issue

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