REVIEW

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Using statins to treat inflammation in acute coronary syndromes: Are we there yet?

ABSTRACT

Inflammation and oxidative damage play direct roles in coronary artery disease. C-reactive protein (CRP) is currently the best available marker of inflammation, and statins can potentially reduce coronary inflammation. Until now, CRP testing has been somewhat controversial in the context of cardiovascular disease, as has statin treatment specifically to treat inflammation. However, three recent studies showed that early and aggressive treatment with statins reduces future cardiovascular and cerebrovascular events in patients with acute coronary syndromes; another study showed that aggressive statin treatment leads to regression of stable coronary artery disease. In all the studies, the benefit correlated with reductions in CRP.

KEY POINTS

Statins lower the risk of cardiovascular events beyond the expected reduction attributable to cholesterol-lowering alone. The extra benefit of statins may be explained by their potent anti-inflammatory and antioxidant effects.

Intensive statin therapy slows or reverses plaque progression in coronary arteries.

Early and aggressive statin therapy in patients with acute coronary syndromes reduces the risk of future cardiovascular events.

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RECENT STUDIES provide strong evidence that patients with acute coronary syndromes should be treated early and aggressively with statins to reduce the risk of future cardiovascular and cerebrovascular events. The early benefit of statins may be linked more strongly to their anti-inflammatory, antioxidant, and plaque-stabilizing effects than to their cholesterol-lowering effects.

This article reviews three recent randomized studies of high-dose statin therapy in patients with acute coronary syndromes and one study in patients with stable coronary artery disease, and discusses the implications of these studies for the treatment of inflammation in cardiovascular disease.

INFLAMMATION, ATHEROGENESIS, AND STATINS

Although many options are available for diagnosing and treating established cardiovascular risk factors such as hypertension and diabetes mellitus, few are available that specifically target inflammation.[1–4]

Inflammation plays a direct role in atherogenesis, from foam cell formation to plaque progression and rupture.[1,5,6] Mechanisms for the direct association between C-reactive protein (CRP) and coronary artery disease have been described previously in the *Cleveland Clinic Journal of Medicine*.[7,8] A number of studies, including several meta-analyses, have shown that CRP, measured by a highly sensitive assay, predicts cardiovascular risk and is the marker of choice to assess inflammation.[4,7,9–11]

TABLE 1

Four recent trials of statins in high doses

	MIRACL	A TO Z	PROVE IT-TIMI 22	REVERSAL
No. of patients	3,086	4,497	4,162	502
Indication	Acute coronary syndromes	Acute coronary syndromes	Acute coronary syndromes	Stable coronary artery disease
Treatments	Atorvastatin 80 mg vs placebo	Simvastatin 40 mg followed by 80 mg vs placebo followed by simvastatin 20 mg	Atorvastatin 80 mg vs pravastatin 40 mg	Atorvastatin 80 mg vs pravastatin 40 mg
Follow-up period	16 weeks	6–24 months	18–36 months	18 months
End points	Clinical composite*	Clinical composite†	Clinical composite‡	Change in atheroma volume
Change in low-density lipoprotein cholesterol (%)				
High-dose group	–42	–41	–42	–47
Control group	+9	–27	–10	–27
Change in C-reactive protein (%)				
High-dose group	–83	–93	–89	–36
Control group	–74	–91	–83	–3

MIRACL = Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering trial,[27] PROVE IT-TIMI 22 = the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trial,[30] A to Z = Aggrastat to Zocor trial,[32] REVERSAL = Reversal of Atherosclerosis With Aggressive Lipid Lowering study[8,24–26]

* Death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia.

† Cardiovascular death, nonfatal myocardial infarction, readmission for acute coronary syndromes, and stroke.

‡ Death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization or revascularization, and stroke.

However, some experts are skeptical of CRP's role in coronary artery disease risk assessment, and believe that measuring CRP adds little to the information gained by assessing traditional cardiovascular risk factors.[12,13] Kushner and Sehgal[13] argue that CRP is not an effective screening test for cardiovascular risk because the test is not accurate (elevated levels carry a low risk ratio for coronary disease), it is not reliable (CRP levels vary widely in the same patient), and there is no effective treatment that will reduce risk if elevated levels are detected. Indeed, elevated CRP is a nonspecific sign, and better tests are needed. However, in light of recent randomized trials (see below), the opportunity to identify and treat patients who have heightened inflammation has never been more appealing.

Benefit of statins beyond lipids

Multiple trials have shown that statin treatment substantially decreases the rates of cardiovascular morbidity and mortality in patients with cardiovascular disease.[14,15] Although statins reduce low-density lipoprotein cholesterol (LDL-C), many believe that their benefits cannot be fully explained by their lipid-lowering effects; anti-inflammatory and antioxidant properties likely also play critical roles.[16,17] Statins are most likely to reduce the rate of clinical events when used in high doses in patients with heightened inflammation (ie, those with elevated CRP).[18]

Statins may reduce risk by several mechanisms other than lipid-lowering.[19] They decrease superoxide production from NADPH oxidase 1 in vascular smooth muscle cells, reduce the inflammatory cell burden within atherosclerotic plaques, and potentially promote up-regulation of endothelial nitric oxide synthase, leading to more nitric oxide formation.[16] They also suppress inflammation and oxidation systemically by inhibiting isoprenylation of Rac, a key component of the

NADPH oxidase complex of both leukocytes and vascular endothelial cells.[17,19–21]

Although these "pleiotropic" effects of statins are not in question, some authors question whether they are clinically relevant. LaRosa,[22] in a recent editorial commenting on a meta-regression analysis by Robinson et al,[23] asserted that these effects do not contribute to an additional cardiovascular and cerebrovascular benefit beyond LDL-C reduction and concluded that the burden of proof that these effects are of clinical value has not yet been met.

However, all of the studies in the meta-analysis by Robinson et al were in patients with stable coronary artery disease. The anti-inflammatory effects of statins may be more clinically relevant in acute coronary syndromes and when the drugs are used in higher doses, as we will see.

IMPORTANT STATIN TRIALS

Four recent trials of statins are discussed below and summarized in TABLE 1.

Many believe that lipid-lowering does not fully explain the benefits of statins

REVERSAL: Reducing CRP reduces plaque

The Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL) study was the first randomized trial that used intravascular ultrasonography to establish that inflammation is directly associated with atherosclerotic plaque burden and progression.[8,24–26]

The study enrolled more than 500 patients with stable angina, at least 20% stenosis on coronary angiography, and an LDL-C level of 125 to 210 mg/dL after 4 to 10 weeks of a statin-free washout period. The patients were randomly assigned to receive either moderate statin treatment (pravastatin 40 mg/day) or intensive statin treatment (atorvastatin 80 mg/day). At baseline and after 18 months of therapy, blood levels of lipoproteins and CRP were measured and patients underwent intravascular ultrasonography of the longest and least angulated target vessel. Atheroma volume was calculated as the sum of the differences between the external elastic membrane and lumen areas across all slices.

After treatment, CRP and LDL-C levels were significantly lower than at baseline ($P < .001$). Reductions were more pronounced in the intensive-therapy group. Plaque regression strongly correlated with CRP reduction and less strongly correlated with LDL-C reduction. Patients with the greatest reduction in CRP levels had the most plaque regression.

MIRACL: Early aggressive statin therapy reduces risk in acute coronary syndromes

The Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) trial[27] was the first large study to investigate whether starting high-dose atorvastatin therapy early after an acute coronary syndrome event reduces the risk of recurrent events.

More than 3,000 patients presenting with unstable angina or myocardial infarction without ST-segment elevation were randomized to start treatment within 24 to 96 hours with either atorvastatin 80 mg or placebo.

At 16 weeks, the rate of the composite end point (death, nonfatal myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic ischemia requiring emergency hospitalization) was 16% lower in the active treatment group than in the placebo group, largely due to fewer events of recurrent symptomatic ischemia. There were also significantly fewer strokes in the active treatment group.[28]

Interestingly, the treatment groups began to separate in their survival curves for the composite end point at about 4 weeks; previous secondary prevention trials of statin therapy in patients with stable coronary disease had primary end point curves that did not separate for up to 1 year.

CRP levels declined from baseline in both groups, but they declined significantly more in the atorvastatin group than in the placebo group.[29] Unfortunately, no data are available regarding whether the CRP reduction was associated with the reduction in clinical end points.

PROVE IT-TIMI 22: More evidence of benefit

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI

22) trial also examined high-dose statin therapy in patients with acute coronary syndromes.[30] The investigators sought to determine if aggressive atorvastatin therapy (with the goal of reducing LDL-C levels to about 70 mg/dL) was better than moderate pravastatin therapy (with the more traditional goal of 100 mg/dL or less).

More than 4,000 patients presenting with an acute coronary syndrome event were randomized to treatment with either atorvastatin 80 mg or pravastatin 40 mg and followed for up to 36 months; the mean was 24 months. The primary end point was a composite of all-cause mortality and nonfatal major adverse cardiovascular events (myocardial infarction, stroke, and unstable angina requiring rehospitalization).

Patients on aggressive therapy had a 16% lower incidence of the primary end point vs patients on moderate therapy (P = .005). As in the MIRACL trial, event curves began to separate after only several weeks of treatment.

Patients who achieved lower CRP levels at any level of LDL-C had better clinical outcomes than patients with elevated CRP.[31] Those with CRP levels lower than 1 mg/L and LDL-C less than 70 mg/dL had the lowest risk of adverse events. Variation in CRP was largely unaccounted for by variation in LDL-C. Atorvastatin 80 mg was much more effective than pravastatin 40 mg in reducing both LDL-C and CRP concentrations to goal levels rapidly and durably, although most patients did not achieve both an LDL-C level lower than 70 mg/dL and a CRP level lower than 1 mg/dL with either regimen.

A to Z: Early aggressive therapy has long-term benefits

Phase Z of the Aggrastat to Zocor (A to Z) trial compared an aggressive dosing strategy with a more moderate and delayed dosing strategy in patients presenting with an acute coronary syndrome.[32] The goals of the trial were similar to those of the PROVE IT-TIMI 22 trial.

Nearly 4,500 patients were randomized. The aggressive-treatment group received simvastatin 40 mg/day for 1 month followed by 80 mg/day; the conservative-treatment group received placebo for 4 months followed by simvastatin 20 mg/day. Patients were followed for 6 to 24 months. The primary end point was a composite of cardiovascular death and nonfatal major cardiovascular events (myocardial infarction, readmission for acute coronary syndrome, and stroke).

Patients in the aggressive-treatment group had a 11% lower rate of the primary end point compared with the conservative-treatment group, but the difference was not statistically significant. In contrast to the MIRACL and PROVE IT-TIMI 22 trials, the event curves did not begin to separate early on: in fact, in a post hoc analysis, no benefit from active therapy vs placebo was detected in the first 4 months. After that, there was a statistically significant 25% reduction of the primary end point in the aggressive-treatment group.

The authors hypothesized that the apparent lack of an early benefit may have been due to a lower event rate than anticipated, which reduced the power of the study. Wiviott et al[33] compared PROVE-IT and A to Z and concluded that a number of factors, including chance, could account for the different results.

LESSONS FROM THE TRIALS

Others argue that the pleiotropic effects of statins are not clinically important

The REVERSAL study provided in vivo evidence for a direct association, though modest, between CRP and plaque burden.

The MIRACL and PROVE IT trials extended REVERSAL's findings to the clinical realm and provide a strong argument for high-dose atorvastatin therapy in patients with acute coronary syndromes. The trials' results lend credence to the role of CRP and inflammation in coronary artery disease: patients presented with markedly elevated CRP levels that were quickly and dramatically reduced by high-dose atorvastatin more than with moderate-dose pravastatin or placebo. The early separation of event curves was driven mainly by fewer events of recurrent symptomatic ischemia, suggesting that early benefit may result from quiescence of inflamed or ruptured atherosclerotic plaque rather than LDL-lowering alone.

The A to Z trial used simvastatin in two different dosing strategies, and the difference in the primary end point was not statistically significant. At first glance, this finding sug-

TABLE 2

C-reactive protein and low-density lipoprotein cholesterol levels in the four trials

TRIAL AND TREATMENT	BASELINE	1 MONTH	4 MONTHS	8 MONTHS	18–24 MONTHS
C-reactive protein (mg/dL)					
MIRACL					
Placebo	11.0	—	2.9	—	—
Atorvastatin 80 mg	11.5	—	1.9	—	—
A to Z					
Placebo, then simvastatin 20 mg	20.4	2.5	2.3	1.8	—
Simvastatin 40 mg, then 80 mg	20.1	2.4	1.7	1.5	—
PROVE IT-TIMI 22					
Pravastatin 40 mg	12.2	2.3	2.1	—	2.1
Atorvastatin 80 mg	11.9	1.6	1.3	—	1.3
REVERSAL					
Pravastatin 40 mg	3.0	—	—	—	2.9
Atorvastatin 80 mg	2.8	—	—	—	1.8
Low-density lipoprotein cholesterol (mg/dL)					
MIRACL					
Placebo	124	—	135	—	—
Atorvastatin 80 mg	124	—	72	—	—
A to Z					
Placebo, then simvastatin 20 mg	111	122	124	77	81
Simvastatin 40 mg, then 80 mg	112	68	62	63	66
PROVE IT-TIMI 22					
Pravastatin 40 mg	106	—	—	—	95
Atorvastatin 80 mg	106	—	—	—	62
REVERSAL					
Pravastatin 40 mg	150	—	—	—	110
Atorvastatin 80 mg	150	—	—	—	79

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gests that all statins may not be equally beneficial. But another explanation for this apparent discrepancy may be found by looking at the CRP data (TABLE 2).

In PROVE IT at 1 month, CRP levels were significantly lower (30%) in the high-dose atorvastatin group than in the low-dose pravastatin group, and the difference persisted throughout the trial. In the MIRACL trial, the CRP levels in the two treatment groups differed by 34% at 4 months.

In A to Z, however, the CRP levels at 1 month were nearly identical, and at 4 months the difference was 26%. A median LDL-C level of less than 70 mg/dL in the intensive therapy group was attained at 1 month and maintained throughout the trial. The apparent lack of early benefit may be explained by the lack of a significant difference in CRP with this dosing strategy.

By the end of the A to Z trial, the median CRP level in the intensive treatment group was significantly less than 2 mg/L. This finding, plus the findings of the post hoc analysis suggesting late benefits, indicate that high-dose simvastatin may yet be beneficial if given "up front" rather than in the more conservative strategy. But the rate of rhabdomyolysis in the A to Z trial with simvastatin 80 mg was high (0.4%), and cases of frank rhabdomyolysis were reported, which should give us pause, particularly in light of the much lower inci-

dence of these events in the trials using high-dose atorvastatin.

Ongoing trials should more definitively address efficacy and safety concerns surrounding high-dose simvastatin therapy and its use in acute coronary syndrome.[34] The Studies of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) secondary prevention trial is evaluating the use of simvastatin 80 mg vs 20 mg in more than 12,000 patients. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT) is evaluating the use of either simvastatin 40 mg alone or simvastatin 40 mg combined with ezetimibe 10 mg in more than 10,000 patients with acute coronary syndrome.

TAKE-HOME POINTS

The data linking inflammation and oxidative damage with coronary artery disease and acute coronary syndromes are now irrefutable. The trials discussed in this review illuminate the role of inflammation in atherosclerosis and provide solid evidence for the benefit of targeting inflammation to slow plaque progression and improve clinical outcomes.

To date, there are no widely accepted and established markers of inflammation for cardiovascular disease and no known therapeutic measures to modulate coronary inflammation. CRP is currently the best marker of inflammation, and in addition to weight loss, exercise, and smoking cessation, statins are the best therapeutic option to modulate inflammation.

New avenues for diagnosing and treating coronary inflammation are on the horizon. In the next 10 years, myeloperoxidase and nitrotyrosine may emerge as promising new markers of inflammation. In addition, novel specific molecules that inhibit isoprenylation and other key components of the inflammatory cascade may one day offer new treatment options.

REFERENCES

1. **Shishehbor MH, Bhatt DL.** Inflammation and atherosclerosis. Curr Atheroscler Rep 2004; 6:131–139.
2. **Bhatt DL, Topol EJ.** The arterial inflammation hypothesis [letter]. Arch Intern Med 2002; 162:2249–2250; author reply 2250–2251.
3. **Bhatt DL, Topol EJ.** Need to test the arterial inflammation hypothesis. Circulation 2002; 106:136–140.
4. **Shishehbor MH, Hazen SL.** Inflammatory and oxidative markers in atherosclerosis: relationship to outcome. Curr Atheroscler Rep 2004; 6:243–250.
5. **Libby P, Ridker PM, Maseri A.** Inflammation and atherosclerosis. Circulation 2002; 105:1135–1143.
6. **Mills R, Bhatt DL.** The yin and yang of arterial inflammation. J Am Coll Cardiol 2004; 44:50–52.
7. **Shishehbor MH, Bhatt DL, Topol EJ.** Using C-reactive protein to assess cardiovascular disease risk. Cleve Clin J Med 2003; 70:634–640.
8. **Patel VB, Robbins MA, Topol EJ.** C-reactive protein: A 'golden marker' for inflammation and coronary artery disease. Cleve Clin J Med 2001; 68:521–524, 527–534.
9. **Pearson TA, Mensah GA, Alexander RW, et al; Centers for Disease Control and Prevention and American Heart Association.** Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107:499–511.
10. **Chan AW, Bhatt DL, Chew DP, et al.** Early and sustained survival benefit associated with statin therapy at the time of percutaneous coronary intervention. Circulation 2002; 105:691–696.
11. **Chan AW, Bhatt DL, Chew DP, et al.** Relation of inflammation and benefit of statins after percutaneous coronary interventions. Circulation 2003; 107:1750–1756.
12. **Danesh J, Wheeler JG, Hirschfield GM, et al.** C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004; 350:1387–1397.
13. **Kushner I, Sehgal AR.** Is high-sensitivity C-reactive protein an effective screening test for cardiovascular risk? Arch Intern Med 2002; 162:867–869.
14. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344:1383–1389.
15. **Heart Protection Study Collaborative Group.** 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.
16. **Liao JK.** Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol 2005; 96:24F–33F.
17. **Shishehbor MH, Brennan ML, Aviles RJ, et al.** Statins promote potent systemic antioxidant effects through specific inflammatory pathways. Circulation 2003; 108:426–431.
18. **Topol EJ.** Intensive statin therapy—a sea change in cardiovascular prevention. N Engl J Med 2004; 350:1562–1564.
19. **Shishehbor MH, Hazen SL.** Antioxidant studies need a change of direction. Cleve Clin J Med 2004; 71:285–288.
20. **Laufs U, La Fata V, Plutzky J, Liao JK.** Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998; 97:1129–1135.
21. **Liao JK.** Isoprenoids as mediators of the biological effects of statins. J Clin Invest 2002; 110:285–288.
22. **LaRosa JC.** At the heart of the statin benefit [editorial]. J Am Coll Cardiol 2005; 46:1863.
23. **Robinson JG, Smith B, Maheshwari N, Schrott H.** Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. J Am Coll Cardiol 2005; 46:1855–1862.
24. **Nissen SE, Tuzcu EM, Schoenhagen P, et al; Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators.** Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005; 352:29–38.
25. **Karha J, Bhatt DL.** Plaque regression—a new target for anti-atherosclerotic therapy. Am Heart J 2005; 149:384–387.
26. **Nissen SE, Tuzcu EM, Schoenhagen P, et al; REVERSAL Investigators.** Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291:1071–1080.

27. **Schwartz GG, Olsson AG, Ezekowitz MD, et al; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators.** Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001; 285:1711–1718.
28. **Waters DD, Schwartz GG, Olsson AG, et al; MIRACL Study Investigators.** Effects of atorvastatin on stroke in patients with unstable angina or non-Q-wave myocardial infarction: a Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) substudy. Circulation 2002; 106:1690–1695.
29. **Kinlay S, Schwartz GG, Olsson AG, et al; MIRACL Study Investigators.** High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. Circulation 2003; 108:1560–1566.
30. **Cannon CP, Braunwald E, McCabe CH, et al; 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 2004; 350:1495–1504.
31. **Ridker PM, Cannon CP, Morrow D, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators.** C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352:20–28.
32. **de Lemos JA, Blazing MA, Wiviott SD, et al; A to Z Investigators.** Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004; 292:1307–1316.
33. **Wiviott SD, de Lemos JA, Cannon CP, et al.** A tale of two trials: a comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE IT-TIMI 22. Circulation 2006; 113:1406–1414.
34. **MacMahon M, Kirkpatrick C, Cummings CE, et al.** A pilot study with simvastatin and folic acid/vitamin B12 in preparation for the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). Nutr Metab Cardiovasc Dis 2000; 10:195–203.

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