Early Statin Therapy in Acute Coronary Syndromes

The Successful Cycle of Evidence, Guidelines, and Implementation

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That statins should be prescribed for patients before hospital discharge after an episode of acute coronary syndrome (ACS) is a Level of Evidence: 1A recommendation of the American College of Cardiology/American Heart Association Joint Task Force. This level of recommendation is based upon 2 clinical trials: the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) and PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trials. In the MIRACL trial, 3,086 patients with unstable angina or non-Q-wave myocardial infarction were randomized within 4 days of the event to atorvastatin 80 mg/day or to placebo and followed for 16 weeks. The primary composite end point occurred in 14.8% of atorvastatin patients and 17.4% of placebo patients, a 16% relative risk reduction (p = 0.048). In the PROVE-IT trial, 4,162 patients hospitalized with an ACS within the preceding 10 days were randomized to atorvastatin 80 mg/day or pravastatin 40 mg/day and were followed for a mean of 24 months. The primary event rate was 22.4% in the atorvastatin group and 26.3% in the pravastatin group, a 16% relative risk reduction (p = 0.005). A strong trend toward a reduction in total mortality was seen in the atorvastatin group (2.2% vs. 3.2%, p = 0.07). Using a composite end point of death, myocardial infarction, and rehospitalization for ACS, the difference between the treatment groups is already statistically significant at 30 days and remains so throughout the follow-up period. Comprehensive treatment programs in ACS patients that include initiation of statins before hospital discharge have been shown to improve outcomes such as recurrent myocardial infarction and total mortality at 1 year. Guidelines prove their utility when their implementation improves outcomes across a broad population at risk, such as in this instance. (J Am Coll Cardiol 2009;54:1434–7) © 2009 by the American College of Cardiology Foundation

Delay always breeds danger; and to protract a great design is often to ruin it.
—Don Quixote, Miguel de Cervantes (1)

Guidelines abound. From 1984 to September 2008, the American College of Cardiology/American Heart Association Joint Task Force issued 53 guidelines including 7,196 recommendations (2). Of the 16 current guidelines reporting levels of evidence, only 11% are classified as Level of Evidence: A; that is, a recommendation based on evidence from randomized trials or meta-analyses (2).

In this issue of the Journal, Morrissey et al. (3) criticize the Level of Evidence: 1A recommendation that statins should be prescribed for patients before hospital discharge after an episode of acute coronary syndrome (ACS). We disagree with their conclusions and with their interpretation of the facts. Their choice, to attack this recommendation from among so many easier targets, seems quixotic.

The Context

In more than a dozen large randomized controlled clinical trials involving more than 100,000 patients, statins have consistently reduced the risk of cardiovascular events, across a broad spectrum of patients at risk. In 3 trials of patients with stable coronary heart disease (CHD), statins reduced not only cardiovascular end points but also total mortality (4–6). More aggressive low-density lipoprotein cholesterol (LDL-C) lowering with higher doses of more potent statins, compared with lower doses or less potent statins, has been shown to provide incremental risk reduction in patients with stable CHD (7,8).

Survivors of ACS will have stable CHD within 6 to 12 months and will benefit from long-term statin treatment. Morrissey et al. (3) agree that these patients should be treated long-term, but disagree that treatment should begin in hospital. The evidence clearly indicates that compliance with treatment is higher and long-term outcomes better when statins are begun before hospital discharge (9–11).

The Standard

Coronary heart disease has evolved dramatically over the past 40 years, and clinical trials of CHD have evolved as well. From 1966 to 1969 the Coronary Drug Project...
enrolled men ages 30 to 64 years who had suffered a myocardial infarction (MI) a median of 23 months previously, and who were New York Heart Association functional class I to II (12). In the placebo group after 6.2 years of follow-up, 25.9% of the patients had died and 14.7% of them had experienced another MI. With high rates of hard end point events such as this, clinical trials could be performed with reasonable sample sizes and follow-up periods. Over the ensuing decades, event rates have fallen dramatically; for example, in a recent large trial of patients with stable CHD followed for 4.9 years, the total mortality rate was 5.6% and the rate of nonfatal MI was 6.2% in the control group (7). Event rates in recent trials have even been substantially lower than the rates predicted by the Framingham Risk Score (13).

As death and ST-segment elevation MI have become less common, other end points such as non–ST-segment elevation MI, hospitalization for unstable angina, hospitalization for heart failure, and coronary revascularization have become more common. These “softer” events are expensive and worsen quality of life. To ignore them is not reasonable. Treatments that reduce these events are clinically useful. Due to the evolution of CHD, we now accept as a primary end point a composite of clinically important events that represent the current reality of the disease.

The Evidence

In the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial, 3,086 patients with unstable angina or non–Q-wave MI were randomized within 4 days of the event to atorvastatin 80 mg/day or to placebo and followed for 16 weeks (14). The primary end point, a composite of death, MI, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia with objective evidence requiring emergency hospitalization, occurred in 14.8% of atorvastatin patients and 17.4% of the placebo patients (hazard ratio [HR]: 0.84, 95% confidence interval [CI]: 0.70 to 1.00, p = 0.048).

The statement by Morrissey et al. (3) that “an unplanned interim analysis was performed in MIRACL without adjustment of p value in the reported results” is not correct (Elliott Rapaport, Chair, MIRACL Data and Safety Monitoring Board, personal communication, May 4, 2009). As clearly stated in the paper (3): “The study protocol specified 3 interim analyses of safety and efficacy by the data and safety monitoring board. A significance level of p = 0.001 was used for each interim analysis, with a significance level for the final analysis adjusted to p = 0.049 to preserve the overall type I error rate at p = 0.05.”

In the PROVE-IT (Pravastatin or Atorvastatin with Aggressive Cholesterol Lowering) trial, 4,162 patients hospitalized with an ACS within the preceding 10 days were randomized to atorvastatin 80 mg/day or pravastatin 40 mg/day and were followed for a mean of 24 months (15). The primary end point consisted of death, MI, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia with objective evidence requiring emergency hospitalization, occurred in 14.8% of atorvastatin patients and 17.4% of the placebo patients (HR: 0.84, 95% CI: 0.74 to 0.95, p = 0.005). A strong trend toward a reduction in total mortality was seen in the atorvastatin group (2.2% vs. 3.2%, p = 0.07).

The results of the PROVE-IT trial are particularly noteworthy because the comparator group was treated with pravastatin 40 mg/day, the drug and dose that significantly reduced the primary end point in 4 older large randomized placebo-controlled trials.

Time to Benefit

Clinical trials are not designed to demonstrate when the benefit of treatment begins. However, as shown in Figure 1, the cumulative hazard ratios for the primary end point in the PROVE-IT trial are reduced by approximately the same amount from 15 days to 4 months, with the difference becoming statistically significant at the later point (16). Using a composite end point of death, MI, and rehospitalization for ACS, the difference between the treatment groups is already statistically significant at 30 days and remains so throughout the follow-up period (16). Clearly, early initiation of treatment provides near immediate benefit.

Relationship Between Benefit and LDL-C Levels

In the MIRACL trial, patients with a baseline LDL-C below the median value of 121 mg/dl benefited from atorvastatin (HR: 0.77, 95% CI: 0.59 to 0.98), and baseline LDL-C was not a predictor of events (14,17). In the PROVE-IT trial, lower achieved LDL-C levels were also associated with reduced risk in the PROVE-IT trial: patients with LDL-C levels ≤125 mg/dl, where a 34% event reduction was seen, compared with only 7% among patients with lower LDL-C levels (15). This disparity between the MIRACL and PROVE-IT trials may be due to the different durations of follow-up in the trials, or to the fact that 25% of PROVE-IT patients were on existing statin therapy at baseline.

In the TNT (Treating to New Targets) trial, LDL-C levels on treatment were a strong predictor of events, with lower event rates seen at the lowest attained LDL-C levels (18). Lower achieved LDL-C levels were also associated with reduced risk in the PROVE-IT trial: patients with LDL-C levels ≤40 mg/dl had a relative risk of 0.61 (95% CI: 0.40 to 0.91) compared with patients with an on-treatment LDL-C of 80 to 100 mg/dl (19).
Adverse Effects of High-Dose Statins

As pointed out by Morrissey et al. (3), the 80-mg dose of simvastatin was associated with a much higher incidence of myopathy than the 20-mg dose in both the A to Z (Aggrastat to Zocor) (20) and SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) (21) trials. On the other hand, as shown in Table 1, the 80-mg dose of atorvastatin has been given to 18,696 patients in clinical trials, usually for between 4 and 5 years, with an overall incidence of hepatic enzyme elevation of 1.43%, and only 4 patients with creatine kinase elevations >10 times the upper limit of normal. The incidence of adverse effects is likely to be higher in patients not participating in a clinical trial; nevertheless, these data indicate that 80 mg of atorvastatin is probably safer than 81 mg of aspirin.

Implementation

Comprehensive treatment programs in ACS patients that include initiation of statins before hospital discharge have been shown to improve outcomes. In the CHAMP (Cardiac Hospitalization Atherosclerosis Management Program) trial (9), the proportion of ACS patients who received a statin at hospital discharge increased from 6% to 86% and the proportion achieving an LDL-C of ≤100 mg/dl increased from 6% to 58%. This was associated with a reduction in recurrent MI and total mortality at 1 year. A guidelines-based program that included lipid-lowering drugs also improved outcomes in the ACC GAP (American College of Cardiology Guidelines Applied in Practice) project (10). Statins at hospital discharge improve outcomes even in ACS patients with LDL-C levels <100 mg/dl (11).

Guidelines prove their utility when their implementation improves outcomes across a broad population at risk.

The proof of the pudding is in the eating.

—Don Quixote, Miguel de Cervantes (22)

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REFERENCES


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