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# Statins in acute coronary syndromes: Start them in the hospital

## ABSTRACT

Most patients with an acute coronary syndrome should start taking a statin drug while still in the hospital if they are not already taking a statin, according to recent studies. In this situation, a statin drug should be started if the low-density lipoprotein (LDL) value is 130 mg/dL or higher, or perhaps even 100 mg/dL or higher.

## KEY POINTS

Several clinical trials found that statin drugs, started in the hospital, reduced the recurrence of acute coronary events both during and after hospitalization for acute coronary syndromes.

The benefit of statins in acute coronary syndromes may be partly due to nonlipid effects, such as decreasing thrombus formation, improving fibrinolysis, inhibiting platelet reactivity and aggregation, improving endothelial function, reducing thromboxane $A_2$ production, and reducing cytokine formation.

Starting statins before discharge from the hospital encourages long-term compliance.

MOST PATIENTS with acute coronary syndromes should start taking a statin drug while still in the hospital if they are not already taking one, according to recent studies.

Current guidelines from the American College of Cardiology and the American Heart Association[1] call for lipid-lowering therapy *after* hospital discharge for patients with unstable angina or non-Q-wave myocardial infarction (MI) whose low-density lipoprotein (LDL) values at discharge are at 130 mg/dL or higher. However, most of the recent studies found that patients who were taking a statin when they were discharged had lower rates of death and ischemic events in the ensuing months than patients discharged not taking a statin.

Starting statin therapy before hospital discharge would also strongly encourage long-term compliance,[2,3] which at present remains poor. Further, statin therapy is rarely associated with adverse effects.[2] Therefore, prudence would dictate starting LDL-lowering therapy before discharge in patients with LDL values above 130 mg/dL, or perhaps even above 100 mg/dL, as now recommended by the third Adult Treatment Panel of the National Cholesterol Education Program (ATP III).[4]

We would go even farther. After the preliminary data presented in this review are formally published and examined, we would encourage the writers of future guidelines to consider recommending statin drugs for *all* patients with acute coronary syndromes, regardless of LDL level, as the standard of care.

## STATINS AS PREVENTION

Multiple studies showed that statins safely reduce cardiovascular risk both in healthy peo-

ple (as primary prevention)[5,6] and in people who already have cardiovascular disease (as secondary prevention).[7–9] In all of these studies, patients took statins or placebo for a period of years, with repeat visits mandated by the study protocols. Patients with a recent history of acute coronary events were excluded.

In five of the major studies,[5–9] patients taking statins had a significantly lower incidence of clinical events (unstable angina, MI, or death), and no study reported a significant excess of adverse events with statin treatment. However, the benefit became statistically significant only after 1 to 2 years of treatment.

## NONLIPID EFFECTS OF STATINS

Some pathophysiologic data suggest that statins are also beneficial in the acute setting. For example, in the short term (weeks to months) statins have been shown to:

- Decrease thrombus formation[10,11]
- Increase fibrinolysis
- Inhibit platelet reactivity and aggregation[10–13]
- Reduce thromboxane $A_2$ production[14]
- Improve endothelial function in patients with coronary artery disease[15,16]
- Possibly stabilize plaques and make atheromas less susceptible to rupture by reducing cholesterol synthesis by macrophages,[17] decreasing inflammatory cells,[18] reducing matrix metalloproteinase activation,[17] and promoting collagen accumulation in the fibrous cap[19]
- Reduce levels of C-reactive protein, an inflammatory marker and predictor of adverse cardiovascular outcomes.[20]

These findings led to targeted clinical trials and database reviews of the effect of giving statins within days of an acute event.

**Current guidelines on treating acute coronary syndromes may need to be changed**

## THE L-CAD STUDY

In the Lipid-Coronary Artery Disease (L-CAD) study,[21] 70 patients started pravastatin (Pravachol) within 6 days of an acute MI or percutaneous angioplasty for unstable angina, with a goal LDL level of 130 mg/dL or lower. A control group of 56 patients received lipid-lowering therapy after hospital discharge at the discretion of their family physicians.

### Results

At 6 months and 24 months, the minimal lumen diameter, measured by quantitative angiography, was larger than at baseline in the pravastatin group, whereas it decreased in the control group during the same intervals.

At 2 years, the incidence of the combined end point (death, nonfatal MI, need for coronary intervention, stroke, or new onset of peripheral vascular disease) was 23% in the pravastatin group, compared with 52% in the control group (odds ratio 0.28, $P = .005$). The trend was observable at 6 months but was not statistically significant.

### Study limitations

These findings should be interpreted with caution. This was a small, open-label study conducted at only one center. In addition, 23% of the patients in the control group received some kind of lipid-lowering therapy, and 11% of the pravastatin group received a second lipid-lowering medication to achieve the LDL target.

## THE MIRACL STUDY

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study[22] was designed to assess the benefits of robust lipid-lowering immediately after an acute coronary event.

Within the first 24 to 96 hours of a non-Q-wave MI (54% of patients) or unstable angina (46% of patients), 3,806 patients were randomly assigned to receive atorvastatin (Lipitor) 80 mg daily or placebo. The patients were at high risk: 23% had type 2 diabetes mellitus, 55% had hypertension, and 28% currently smoked. The follow-up period was 4 months.

### Results

In the atorvastatin group, LDL values decreased 42% (to 72 mg/dL, from a baseline 124 mg/dL) and triglyceride values decreased 24% (to 139 mg/dL, from a baseline 184 mg/dL), whereas they increased in the placebo group. Changes in HDL levels were minor in both groups.

As expected, more atorvastatin patients developed liver enzyme elevations (2.5% vs

0.6% in the placebo group), but the rate of serious side effects was similar (< 1%) in both groups.

At 16 weeks, the composite primary end point of death, recurrent MI, cardiac arrest with resuscitation, or worsening angina with hospitalization had occurred in 14.8% of the atorvastatin group vs 17.4% of the placebo group (relative risk 0.84; $P = .048$; FIGURE 1). The only end point that reached statistical significance by itself was recurrent symptomatic myocardial ischemia with objective evidence and emergency rehospitalization (6.2% for atorvastatin vs 8.4% for placebo, $P = .02$).

## IS BENEFIT DUE TO LDL-LOWERING OR TO OTHER EFFECTS?

Epidemiologic, observational, and randomized, controlled trials have established the benefits of LDL-lowering per se, but the actual mechanisms by which statins reduce cardiovascular events are not fully understood.

The MIRACL study, for example, found atorvastatin to be beneficial regardless of the baseline LDL level or the percent by which the LDL level was lowered. This may be explained by the nonlipid or "pleiotropic" effects of statins.[23]

On the other hand, patients with baseline LDL levels below 125 mg/dL, which was common in the MIRACL trial, got no cardiovascular benefit from statin treatment in two previous trials, LIPID[9] and CARE.[8] This suggests that statins do something apart from lipid-lowering that make them beneficial in acute coronary syndromes. Similarly, in other studies, simvastatin[24] (Zocor) and pravastatin[25] reduced transplant vasculopathy and mortality after cardiac transplantation without an LDL interaction. These findings may again be explained by the nonlipid effects of statins.

Inhibition of cholesterol biosynthesis is important in reducing the formation of cytokines[26] and may itself be relevant to the nonlipid impact observed.

The MIRACL investigators have not yet reported any data about lipid fractions or about interactions between intermediate particles and HDL in their study. This information could further help characterize the lipid-associated vascular influence of statins.

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## MORE EVIDENCE OF BENEFIT OF EARLY STATIN THERAPY

The FLORIDA trial: Conflicting results. The Fluvastatin on Risk Diminishing After Acute Myocardial Infarction (FLORIDA) trial[27] randomly assigned 540 patients to receive either fluvastatin (Lescol) 80 mg/day or placebo for 1 year. The investigators found no significant difference in ischemic events at 6 weeks and 12 months.

Although this study did not have the statistical power to detect a decrease in mortality with statin treatment, it nevertheless showed a positive trend ($P = .08$) toward fewer deaths among patients with severe ischemia at baseline who received fluvastatin. Overall, the mortality rate at 1 year was 2.6% with fluvastatin vs 4% with placebo ($P$ = NS).

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The FLORIDA trial results have been presented at meetings but not published. Complete publication may help to explain why these results contrast with those of the MIRACL trial.

RIKS-HIA, a registry of post-MI patients in Sweden,[28] noted that 5,528 patients received statin treatment before or at the time of hospital discharge, while 14,071 did not. At 1 year, patients who started taking a statin early had a 25% lower rate of death after adjustment for confounding factors and propensity for statin use ($P$ = .001; FIGURE 2).

A secondary analysis of data from the PURSUIT and GUSTO IIB trials[29] corroborated these findings. Patients with acute coronary syndromes who were receiving lipid-lowering therapy at discharge (n = 3,653) were compared with those not on lipid-lowering therapy at discharge (n = 17,156). Those who were receiving lipid-lowering therapy had a significantly lower rate of all-cause mortality at 30 days (0.5% vs 1.0%, $P$ = .001) and 6 months (1.7% vs 3.5%, $P$ < .0001; FIGURE 3). After adjustment for confounding factors such as the propensity to be prescribed a lipid-lowering agent, the difference was still statistically significant at $P$ = .023.

InTIME-II, OPUS-TIMI 16. Recent data from the Intravenous nPA Treatment of Infarcting Myocardium Early II (InTIME-II) trial,[30] with 14,124 patients, and the Orbofiban in Patients with Unstable coronary Syndromes (OPUS-TIMI 16) trial,[31] with 10,288 patients, also suggest lipid-lowering treatment in the hospital and at discharge is associated with lower mortality 1 year after an acute coronary event, further strengthening the value of early statin use.

A Mayo Clinic retrospective study addressed this issue in 66 patients (mean age 65 years) who presented with an acute MI and either were taking a statin at the time of infarction or received a statin within the first 24 hours of admission.[32] Each of these patients was matched with three MI patients of the same age (within 5 years), gender, and history of coronary artery disease.

Fewer patients in the statin group needed intravenous lidocaine for ventricular arrhythmias ($P$ = .017). The incidence of the combined end point of in-hospital death or reinfarction was 3% in the statin group vs 12% in the control group ($P$ < .05).

However, this was a small retrospective study with a small number of cardiovascular events. Furthermore, 44 of the 66 statin patients were already taking a statin at presentation; therefore, we cannot be sure if the beneficial effect on the combined end point was due to long-term statin therapy, early initiation of statins, or selection bias.

Kayikcioglu et al[33] reported that the combination of pravastatin plus thrombolytic therapy was more beneficial than thrombolytics alone in 150 MI patients during the first 6 hours of the onset of chest pain. The rate of in-hospital death at 6 months was significantly lower ($P$ = .03), as was nonfatal reinfarction at 6 months ($P$ = .01) in the combined-therapy group.

### Routine statins, antibiotics after an acute coronary event

Two large, randomized, controlled clinical trials currently underway are trying to determine if routine statin treatment after acute coronary syndromes reduces cardiovascular events.

PROVE IT. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial is comparing the effect of atorvastatin and pravastatin on cardiovascular events in patients with acute coronary syndromes, and is also studying the role of the antibiotic gatifloxacin (Tequin) in preventing these events. Follow-up will be for 2 years.

A-to-Z. The Aggrastat to Zocor (A-to-Z) trial[34] is evaluating the early aggressive use of simvastatin following both non-ST acute coronary syndromes and ST acute coronary events. It is also enrolling patients who have undergone percutaneous coronary revascularization, a group excluded in the MIRACL study. The investigators will also analyze whether low-molecular-weight heparin or unfractionated heparin affects cardiovascular outcomes in patients with non-ST coronary syndromes treated with aspirin and the glycoprotein IIb/IIIa inhibitor tirofiban (Aggrastat). The follow-up will be 24 to 30 months.

HPS. The recently reported Heart Protection Study (HPS), with 20,000 patients, revealed long-term cardiovascular benefits from initiating statin therapy for high-risk patients with average LDL values, even in those with values less than 100 mg/dL at baseline. The findings were presented at the 2001 American Heart Association Scientific Sessions.

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