ADRIAN W. MESSERLI, MD
Department of Cardiovascular Medicine, The Cleveland Clinic

HERBERT D. ARONOW, MD, MPH*
Department of Cardiovascular Medicine, The Cleveland Clinic

DENNIS L. SPRECHER, MD†
Adjunct staff, The Cleveland Clinic; Director, Dyslipidemia, Discovery Medicine, GlaxoSmithKline; formerly head, Section of Cardiac Prevention, Department of Cardiovascular Medicine, The Cleveland Clinic

THE LESCOL INTERVENTION PREVENTION STUDY (LIPS)

Start all patients on statins early after PCI

ABSTRACT

The Lescol Intervention Prevention Study (LIPS) was the first randomized trial to show a significant reduction in the risk of cardiac events in patients started on fluvastatin immediately after a successful percutaneous coronary intervention. The benefit was independent of baseline cholesterol levels. The results suggest that all patients should be discharged on lipid-lowering therapy after a percutaneous coronary intervention. Currently, this is seldom done.

EVERY TIME A PATIENT undergoes a percutaneous coronary intervention (PCI) and does not start lipid-lowering therapy immediately afterward, a chance is wasted to prevent cardiac events.

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In the United States and elsewhere, lipid-lowering therapy is underused in patients who undergo PCI—and who therefore have a priori coronary artery disease.

This is the take-home point of the Lescol Intervention Prevention Study (LIPS), which confirmed the clinical benefits of starting lipid-lowering therapy early after PCI. These findings, plus other data linking the early start of lipid-lowering therapy to greater long-term compliance, indicate that we should start lipid-lowering therapy in every patient who undergoes PCI.

Lowering lipids in all patients after PCI reduces cardiac events

STATINS AFTER PCI: THE EVIDENCE UP TO NOW

Randomized trials have unequivocally demonstrated the effectiveness of HMG-CoA reductase inhibitors (statins) in reducing cardiac events and deaths in patients with known coronary disease.[1–3] Few patients in these trials had undergone PCI, however, and among those who had, PCI was performed more than 6 months before trial enrollment.[4] As a result, the effect of lipid-lowering therapy initiated immediately after PCI was not known.

However, one observational study found that lipid-lowering therapy started after PCI was associated with a significantly lower mortality rate at 1 year.[5] Other observational studies found lower rates of death or myocardial infarction in patients given lipid-lowering therapy shortly before PCI.[6,7]

In the Fluvastatin Angiographic Restenosis (FLARE) trial,[8] patients randomized to receive fluvastatin for 2 to 4 weeks before PCI had a significantly lower incidence of death and myocardial infarction (a secondary end point) at 40 weeks of follow-up compared with those receiving placebo.

LIPS DESIGN

LIPS was the first prospective randomized double-blind placebo-controlled trial to specifically study the effects of statin therapy on clinical end points after PCI.[9]

*The author has indicated that he serves as a consultant for and is on the speaker's bureau of the Pfizer corporation.
†The author became employed by GlaxoSmithKline corporation after this paper was written and accepted.
This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

Fluvastatin reduces major adverse cardiac events after percutaneous coronary intervention

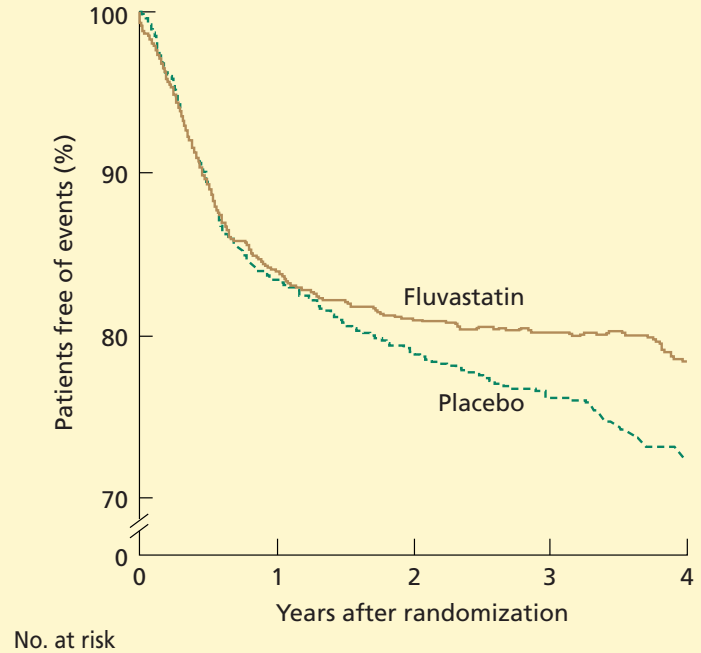

FIGURE 1. Survival free of major adverse cardiac events in the Lescol Intervention Prevention Study (LIPS). Major cardiac events were defined as cardiac death, nonfatal myocardial infarction, or a reintervention procedure.

FROM SERRUYS PWJC, DE FEYTER P, MACAYA C, ET AL. FLUVASTATIN FOR PREVENTION OF CARDIAC EVENTS FOLLOWING SUCCESSFUL FIRST PERCUTANEOUS CORONARY INTERVENTION: A RANDOMIZED CONTROLLED TRIAL. JAMA 2002; 287:3215–3222.

Recruitment for LIPS took place at 77 centers in Europe, Brazil, and Canada between April 1996 and October 1998.

Inclusion criteria

Patients were eligible if they had a total cholesterol level between 135 and 270 mg/dL and a triglyceride level lower than 400 mg/dL. For diabetic patients or patients who presented with a myocardial infarction, the total cholesterol level had to be less than 212 mg/dL.

Exclusion criteria

Patients were excluded if they had any of the following:

- Left ventricular systolic dysfunction (ejection fraction < 30%)
- Poorly controlled hypertension (systolic blood pressure > 180 or diastolic blood pressure > 100 mm Hg despite medical therapy)
- Prior PCI or coronary artery bypass grafting (CABG)
- Renal dysfunction (creatinine > 1.8 mg/dL)
- Clinically significant valvular heart disease
- Idiopathic cardiomyopathy
- Congenital heart disease
- Obesity (body mass index > 35 kg/m^2)
- Concomitant malignancy.

Treatment

Patients were randomized in a blinded fashion to receive either fluvastatin 40 mg twice daily or placebo. The median time until the study drug treatment was started was 2 days after PCI. All patients received dietary counseling before hospital discharge. Decisions about concurrent medical therapy were left to the discretion of the treating physician.

Follow-up

Patients were seen 6 weeks after randomization and then every 6 months for a median of 3.9 years.

A lipid panel was obtained at each follow-up visit, but the investigators were blinded to the results unless the total cholesterol level exceeded 278 mg/dL. If the patient's total cholesterol level remained higher than 278 mg/dL for 3 months or more, he or she was given open-label lipid-lowering therapy.

Investigators were encouraged not to obtain lipid levels at their own laboratories.

Outcomes measured

The primary end point was a composite of cardiac death, nonfatal myocardial infarction, or a reintervention procedure (defined as CABG, repeat PCI, or PCI for a new stenosis).

Secondary end points included:

- The primary end point excluding target lesion revascularization during the first 6 months
- Cardiac, noncardiac, and all-cause mortality

TABLE 1

- Combined cardiac mortality and myocardial infarction
- Combined all-cause mortality and myocardial infarction
- Effects of fluvastatin on lipid levels
- Safety and tolerability of fluvastatin.

RESULTS

Primary end point reduced 22%

Over a median of 3.9 years, the primary end point occurred in 181 (21.4%) of the 844 patients in the fluvastatin group, compared with 222 (26.7%) of the 833 patients in the placebo group (relative risk 0.78, 95% confidence interval 0.64–0.95, $P = .01$).

In addition, the event-free survival time for the primary end point was significantly longer in the fluvastatin group (first quartile of time to first event 1,558 vs 1,227 days, $P = .01$). The difference became apparent at 1.5 years and was maintained over the rest of the trial (FIGURE 1). If target vessel reinterventions (PCI or CABG) during the first 6 months were excluded, the event-free survival curves began to separate by approximately 6 months.

Subgroup analyses. Importantly, the risk reduction with fluvastatin was similar whether baseline levels of low-density lipoprotein (LDL) cholesterol were below or above the median of 132 mg/dL: the relative risk with fluvastatin was 0.74 (95% CI 0.55–0.97) in the lower LDL subgroup and 0.80 (95% CI 0.58–109) in the higher LDL subgroup.

In other subgroup analyses, fluvastatin conferred similar risk reductions in men and women (although this was only statistically significant in men due to the small number of women enrolled), and conferred a benefit in patients with diabetes or multivessel disease (TABLE 1). Patients with multivessel disease had a 37% reduction in the primary end point with fluvastatin, and those with diabetes had a 37% reduction.

Secondary end points

Nonsignificant trends towards reduced cardiac death ($P = .07$) and the combined end point of cardiac death and nonfatal myocardial infarction ($P = .07$) were also seen in fluvastatin-treated patients.

After 6 weeks, LDL cholesterol levels were reduced by 27% with fluvastatin and diet vs 11% with placebo and diet. This effect persisted throughout the trial (FIGURE 2). Fluvastatin had no apparent effect on triglyceride or high-density lipoprotein (HDL) cholesterol levels: triglyceride levels decreased by a median of 14% in both groups, while HDL cholesterol increased by a median of 22% in both groups.

Overall, fluvastatin therapy was well tolerated. For patients in the fluvastatin group, there were no reports of rhabdomyolysis or of creatine kinase elevation greater than 10 times the upper limit of normal. Ten patients in the fluvastatin group developed clinically significant elevation of aminotransferase levels vs 3 patients in the placebo group.

Fluvastatin lowered risk regardless of baseline LDL level

Fluvastatin reduces LDL cholesterol levels after percutaneous coronary intervention

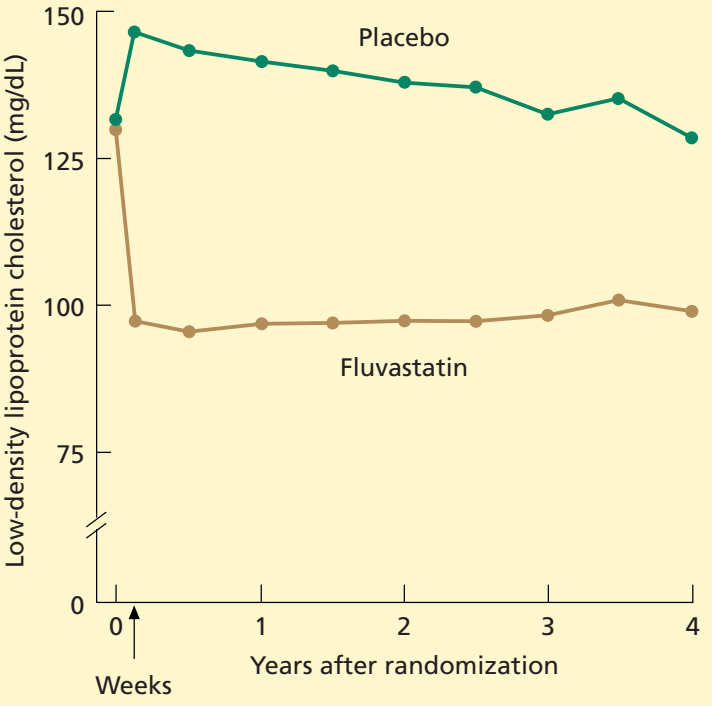

FIGURE 2. Change in low-density lipoprotein (LDL) cholesterol levels in the Lescol Intervention Prevention Study (LIPS).

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The number of deaths not due to cardiac events was nearly identical in the two groups: 23 in the fluvastatin group vs 25 in the placebo group.

INTERPRETATION OF LIPS FINDINGS

The LIPS trial demonstrates that giving a statin early after PCI reduces morbidity and mortality attributed to atherosclerotic disease. Major adverse cardiovascular events were significantly reduced in patients taking fluvastatin over the 3.9 years of follow-up, with the event-free survival curves beginning to diverge at 18 months (and by 6 months when target-vessel revascularization within the first 6 months was excluded).

Importantly, the statin was beneficial regardless of baseline cholesterol levels. This suggests that all patients should be discharged on lipid-lowering therapy after PCI.

The benefits of statin therapy were especially pronounced in patients at high risk, ie, those with diabetes or confirmed multivessel disease. These results support the growing body of evidence that statin therapy is beneficial in all patients with confirmed or suspected coronary vaso-occlusive disease.

Do statins reduce restenosis?

In the first 6 months after PCI, certain patients are prone to develop restenosis in the native vessel or within the stent. This phenomenon is still regarded by many as the Achilles' heel of interventional cardiology, and it complicates up to 40% of angioplasty procedures. Physiologically, it results from smooth muscle cell neoproliferation and extracellular matrix expansion.[10]

In experimental studies, statins have been shown to reduce restenosis,[11] but the clinical evidence to date remains inconclusive.[8,12,13] The LIPS study did not provide specific data on restenosis, but there was no significant difference in rates of reintervention between the two study groups during the first 6 months.

What is the mechanism of benefit?

Although the clinical benefit of statins has primarily been attributed to their lipid-lowering effect, the LIPS patients had a median LDL cholesterol level of only 132 mg/dL. While fluvastatin therapy did reduce LDL cholesterol levels significantly, this reduction alone may not fully account for the risk reduction observed in the fluvastatin group.

Any PCI is, by definition, focally traumatic, with resultant plaque destabilization, endothelial disruption, and superimposed thrombosis. Furthermore, PCI causes local and low-grade systemic inflammation.[14]

Emerging data suggest that statins have pleiotropic properties that could attenuate each of these factors. Specifically, statins stabilize plaque,[15–17] improve endothelial function,[18,19] inhibit platelet aggregation,[20,21] and reduce inflammation.[22,23]

Chronic low-grade inflammation appears to play an important role in atherogenesis,

plaque vulnerability, and vascular thrombosis.[24] C-reactive protein, a hepatically synthesized acute-phase reactant, is widely regarded as a sensitive and objective marker of inflammation. It would have been informative had the LIPS investigators included a subgroup analysis comparing the effects of fluvastatin in patients with elevated serum C-reactive protein levels vs lower levels.

Data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[25] suggest that patients without hyperlipidemia who have elevated levels of C-reactive protein derive greater clinical benefit from statin therapy than those with lower C-reactive protein levels; one might expect statin therapy to be particularly beneficial for patients with greater inflammation at the time of PCI. Preliminary data from the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) study support this latter hypothesis (Herbert Aronow, MD, personal communication, September 2002).

Statins are underused

It has become increasingly clear, despite a wealth of evidence supporting their widespread use, that lipid-lowering medicines are still underused in the United States and abroad. A recent retrospective study of 138,001 patients with acute myocardial infarction admitted to 1,470 US hospitals in the National Registry of Myocardial Infarction noted that only about 32% were discharged on lipid-lowering medications.[26]

In the second European Action on Secondary and Primary Prevention Through Intervention to Reduce Events (EURO ASPIRE 2) study, only 63% of patients with coronary disease from centers in nine European countries were discharged on lipid-lowering therapy.[27]

Further, even when patients are prescribed lipid-lowering drugs, they rarely achieve targets recommended by the National Cholesterol Education Program.[28] In the Lipid Treatment Assessment Program,[29] a survey of frequent prescribers of lipid-lowering therapies, only 13% of their patients with coronary artery disease achieved a target LDL cholesterol level of less than 100 mg/dL.

National Cholesterol Education Program guidelines recommend a target LDL cholesterol level of less than 100 mg/dL in patients with confirmed or suspected coronary heart disease.[28] Therapeutic lifestyle changes are recommended at LDL cholesterol levels of 100 mg/dL or greater, while lipid-lowering therapy is recommended when levels are above 130 mg/dL. Lipid-lowering therapy is optional at LDL cholesterol levels between 100 and 130 mg/dL.

Patients undergoing PCI are presumed to have coronary heart disease. As such, it could be argued that roughly half of the patients in the LIPS trial (median baseline LDL cholesterol 132 mg/dL) qualified for lipid-lowering therapy at baseline, and that most of the remainder would have been eligible to begin lipid-lowering therapy (due to nonpharmacologic treatment failure) during the course of the study.

The overwhelming majority of patients with atherosclerotic vascular disease will ultimately require drug and lifestyle therapy to reach National Cholesterol Education Program targets.[29,30,31]

Benefit is seen early

Importantly, in the LIPS trial, the benefit for patients receiving fluvastatin emerged as early as 6 months after starting therapy if reinterventions were excluded. These data corroborate findings from a number of other studies of survivors of acute coronary syndromes, who also enjoy an early clinical benefit with statin therapy.[32–34]

Patients who undergo PCI are especially receptive to preventive recommendations

Compliance is good after PCI

Patients who undergo PCI, like survivors of acute coronary syndrome events, are usually focused on their disease process and may be especially receptive to adopting new preventive recommendations, including the initiation of lipid-lowering therapy. Starting lipid-lowering therapy in patients while they are still hospitalized after PCI has been associated with improved long-term compliance.[35,36]

Collectively, these findings underscore the importance of starting lipid-lowering therapy early after both PCI and acute coronary syndrome events. Doing so has implications regarding both early clinical outcome and late utilization.

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ADDRESS: *Dennis Sprecher, MD, GlaxoSmithKline, 709 Swedelan Rd, UW2900, King of Prussia, PA 19406.*