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Effect of *Fluvastatin* on Long-Term Outcome After Coronary Revascularization With Stent Implantation

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We assessed the impact of long-term fluvastatin treatment on adverse atherosclerotic cardiac events (cardiac death, myocardial infarction, and revascularization excluding repeat interventions due to restenosis in the first 6 months) in 847 patients (fluvastatin [n = 417] or placebo [n = 430]) with average cholesterol levels treated with stents in the Lescol Intervention Prevention Study (LIPS). During the 4-year follow-up period, fluvastatin significantly decreased total cholesterol and low-density lipoprotein cholesterol levels and decreased the risk of first adverse atherosclerotic cardiac events by 30% compared with placebo (95% confidence interval −49 to −3.4, p = 0.03). ©**2003 by Excerpta Medica, Inc.**

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Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins) decrease the risk of death and major cardiovascular events in patients with chronic heart disease, irrespective of clinical presentation and baseline cholesterol level.[1–4] To date, information regarding the impact of statin treatment after coronary stenting is limited and has generally been derived from observational studies.[5,6] Results from the Lescol Intervention Prevention Study (LIPS)[7,8] have shown that early fluvastatin treatment significantly decreases the risk of major adverse cardiac events in patients with average cholesterol levels after a first successful percutaneous coronary intervention (PCI). We assessed the effects of secondary prevention with fluvastatin in patients with chronic heart disease treated only with stents in the LIPS.

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The LIPS population was recruited from 57 interventional centers in Europe, Canada, and Brazil and consisted of 1,667 patients (age 18 to 80 years) with stable or unstable angina or silent ischemia and average cholesterol levels. Major exclusion criteria included previous PCI or coronary artery bypass graft; high blood pressure (>180/100 mm Hg) despite drug treatment; poor left ventricular function (ejection fraction <30%); severe noncoronary heart disease; severe renal dysfunction (serum creatinine level >1.8 mg/dl [160 μmol/L]); obesity (body mass index >30 kg/m^2); and malignant or other disease resulting in decreased life expectancy. After successfully undergoing their first PCI, patients were randomized to receive either fluvastatin 40 mg twice daily or placebo at hospital discharge for 3 to 4 years. Successful PCI was defined as residual stenosis <50%, with no evidence of myocardial necrosis or need for urgent coronary artery bypass graft. Importantly, decisions regarding revascularization strategy and stenting (elective, for suboptimal result, bail-out) were left to the discretion of the interventional cardiologist. Use of intravascular ultrasound was allowed for diagnostic purposes or for optimization of stent deployment. We evaluated the outcome of the subgroup of patients in whom all lesions were treated with stents. Patients treated with balloon angioplasty alone—or in combination with stenting of ≥1 different lesions—and patients in whom percutaneous interventional devices other than balloon or stent were used were excluded from the analysis. The ethics committee at each participating center approved the trial, and all patients provided informed written consent.

We evaluated patient survival time free of adverse cardiac atherosclerotic events, which were defined as

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TABLE 1 Baseline Patient Characteristics and Demographics

Characteristics & Demographics	Placebo (n = 417)	Fluvastatin (n = 430)
Age (yrs)*	59.5 ± 10.2	59.8 ± 10.0
Men	84.2%	85.6%
Diabetes mellitus	11.5%	11.2%
Systemic hypertension	38.4%	37.4%
Smokers	27.6%	27.4%
Previous myocardial infarction	43.6%	45.3%
Previous stroke	3.4%	2.3%
Clinical presentation		
Unstable angina pectoris	52.7%	55.0%
Stable angina pectoris	36.0%	35.6%
Silent myocardial ischemia	11.4%	9.4%
Body mass index (kg/m^2)*	26.4 ± 3.4	26.7 ± 3.3
Left ventricular ejection fraction† (%)*	60.7 ± 11.7	61.9 ± 11.9
Baseline lipid levels (mg/dl)*		
Total cholesterol	199 ± 33	200 ± 30
LDL cholesterol	132 ± 31	131 ± 29
HDL cholesterol	37 ± 10	38 ± 12
Triglycerides	154 ± 65	153 ± 65

*Values are expressed as mean ± SD.
†Per angiographic assessment.

TABLE 2 Angiographic Characteristics

Characteristics	Placebo (n = 482)	Fluvastatin (n = 505)
No. lesions/patient*	1.2 ± 0.5	1.2 ± 0.5
1	87.1%	85.8%
2	11.0%	12.1%
>2	1.9%	2.1%
Coronary artery treated		
Left anterior descending	54.8%	50.1%
Left circumflex	17.0%	16.0%
Right	28.0%	33.7%
Left main	0.002%	0.002%
Lesion type†		
A	18.7%	15.1%
B1	33.8%	33.1%
B2	34.4%	38.7%
C	13.1%	13.1%
TIMI flow before procedure		
0	0.2%	0.4%
1	0.0%	0.4%
2	0.8%	0.8%
3	97.9%	97.8%
Endoluminal thrombus	1.5%	1.8%

*Values are expressed as mean ± SD; median = 1. †American College of Cardiology/American Heart Association classification.
TIMI = Thrombolysis in Myocardial Infarction.

cardiac death (all deaths unless unequivocally related to a noncardiac cause), nonfatal myocardial infarction (appearance of pathological Q waves that were absent at baseline or a total creatine kinase level >2 times the upper limit of normal with presence of creatine kinase isoenzyme-MB higher than the upper limit of normal), or repeat intervention procedure (either surgical or percutaneous). To decrease the confounding effect of restenosis and to focus on the underlying atherosclerotic disease, new percutaneous or surgical revascularizations performed for lesions treated at the index procedure during the first 6 months of follow-up were excluded from the analysis. This was a predefined end point[8] selected as a result of previous clinical studies that failed to show a significant effect of statin treatment on restenosis.[9–11]

Laboratory measures—including serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and fasting triglyceride levels—were taken from fasting blood samples at a central laboratory (Analytico Medinet, Breda, The Netherlands). Measurements were performed at baseline, at 6 weeks after discharge, and at 6-month intervals thereafter until the conclusion of the study.

All analyses were carried out on an intention-to-treat basis. Continuous variables were expressed as mean ± SD and were compared using Student's unpaired *t* test. Fisher's exact test was used for categoric variables, and Wilcoxon scores were used for categoric variables with an ordinal scale. Discrete variables were expressed as numbers and percentages and were compared in terms of relative risks with 95% confidence intervals. All statistical tests were 2-tailed. Event-free survival distribution was estimated according to the Kaplan-Meier method, and the overall incidence of adverse cardiac atherosclerotic events was compared using the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. The Cox proportional-hazards model was used to assess the risk reduction, and the Cochran-Mantel-Haenszel test was used to compare the incidences of the primary combined end point and its components. Lipid profiles were analyzed in an analysis-of-covariance model incorporating the baseline (at visit 1) as covariate and adding the treatment factors and number of visits (>1) with all possible interaction terms.

In the LIPS, 847 patients (50.5%) were treated exclusively with stenting (fluvastatin [n = 417] or placebo [n = 430]). Baseline clinical (Table 1) and angiographic (Table 2) characteristics in the 2 groups were similar. The average total cholesterol level was 199 ± 33 mg/dl in the placebo group and 200 ± 30 mg/dl in the fluvastatin group (p = NS), and plasma levels of LDL cholesterol, HDL cholesterol, and triglycerides were also similar (Table 1). More than half of the patients in each group presented with unstable angina pectoris. Diabetes mellitus had been diagnosed in 11.5% of placebo-treated patients and in 11.2% of fluvastatin-treated patients. The average number of lesions per patient was 1.2 ± 0.5 in each group, with most patients presenting with only 1 lesion (87% placebo, 86% fluvastatin, p = NS).

At 6 weeks, fluvastatin treatment led to a mean decrease in total cholesterol of 30 mg/dl (−15.1%), whereas a mean increase of 23 mg/dl (+11.5%) was observed in the placebo group. LDL cholesterol levels showed a mean decrease of 32 mg/dl (−24.1%) in the fluvastatin group and a mean increase of 16 mg/dl (+12.0%) in the placebo group (Figure 1). The reduc-

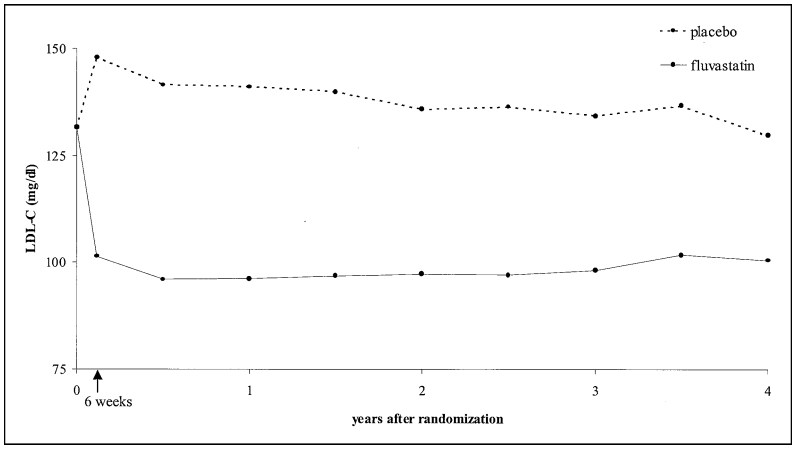

FIGURE 1. Mean change in LDL cholesterol (LDL-C) levels (mg/dl) throughout follow-up in patients treated with stents randomized to receive treatment with either fluvastatin 40 mg twice daily or placebo.

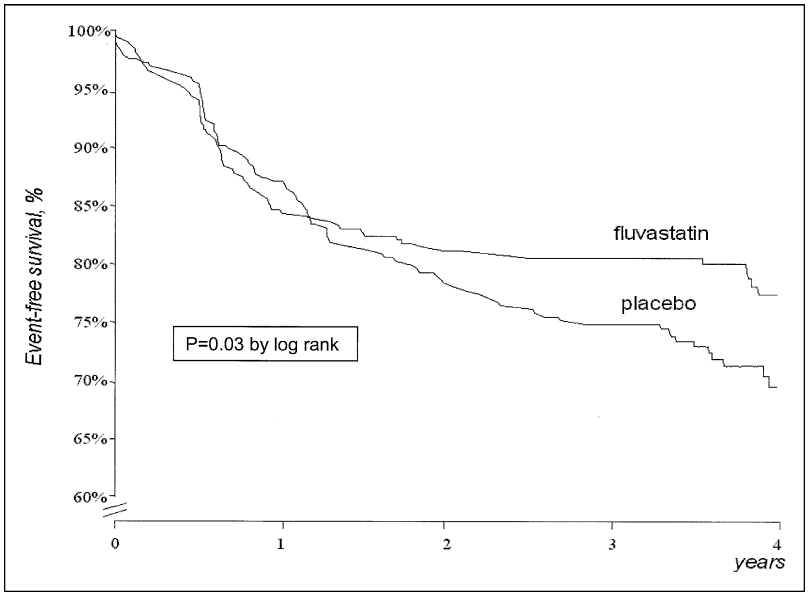

FIGURE 2. Cumulative curves for survival time free of adverse cardiac atherosclerotic events in patients treated with stents randomized to receive either fluvastatin 40 mg twice daily or placebo. Event-free survival distribution was estimated as described in the text, and the p value was obtained from the log-rank test.

tions observed in the fluvastatin group were maintained throughout the study. In contrast, the increases in mean total and LDL cholesterol levels observed at 6 weeks in the placebo group returned almost to baseline levels (Figure 1). No significant changes in HDL cholesterol or triglyceride levels were observed (data not shown).

During 4 years of follow-up, fluvastatin treatment decreased the risk of first adverse cardiac atherosclerotic events by 30% compared with placebo (95% confidence interval −49% to −3.4%, p = 0.03 by log-rank test; Figure 2). The cumulative incidence of adverse cardiac atherosclerotic events during follow-up in both groups is listed in Table 3. According to the Cochran-Mantel-Haenszel test, fluvastatin treatment led to a 5.3% absolute and 25% relative decrease in the total number of events (p = 0.05). Fluvastatin treatment was associated with a trend toward a decreased incidence of each individual component of the composite end point (i.e., cardiac death, myocardial infarction, coronary revascularization), although none of the individual decreases was statistically significant (Table 3). When the data on revascularization were split into target and nontarget lesion revascularization, a significantly lower incidence of nontarget vessel revascularization was observed in the fluvastatin group (relative risk 0.47, 95% confidence interval 0.26 to 0.86, p = 0.01).

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Our findings provide clear evidence that early fluvastatin treatment after coronary stenting is beneficial in patients with average cholesterol levels. In this substudy, fluvastatin treatment led to a significant 30% relative decrease in the risk of first adverse cardiac atherosclerotic events when compared with placebo. This benefit was sustained during 4 years of follow-up.

In a retrospective analysis, Schömig et al[6] observed a decreased 1-year mortality rate in patients treated with coronary stenting who received statins after the procedure compared with those who did not. The retrospective nature of their analysis, and the imbalances in baseline characteristics between the 2 cohorts of patients, did not allow these investigators to draw definitive conclusions. In another nonrandomized study, Walter et al[5] found beneficial effects of statin therapy during a 6-month period after successful coronary stent implantation, suggesting a possible abrogation of the increased risk exhibited by patients with unstable angina pectoris. Statin therapy, however, was initiated only in patients with increased cholesterol levels; therefore, these results could not be extrapolated to patients with "normal" plasma cholesterol levels. The LIPS assessed the incidence of major adverse cardiovascular events in a prespecified analysis, which excluded repeat interventions (PCI or coronary bypass) in the first 6 months of follow-up for lesions treated by the index procedure. In this analysis, fluvastatin significantly decreased the risk of major adverse cardiovascular events by 33% (p <0.001) compared with placebo.[8] In this substudy, the favorable outcome has been confirmed in a patient population treated exclusively with stents, a finding consistent with the hypothesis that most of the benefit of statin therapy derives from

TABLE 3 Cumulative Incidence of Adverse Cardiac Atherosclerotic Events

Events	Placebo (n = 417)	Fluvastatin (n = 430)	Relative risk (95% CI)	p Value
Adverse cardiac atherosclerotic event	90 (21.6%)	70 (16.3%)	0.75 (0.57–1.00)	0.05
Death	8 (1.9%)	5 (1.2%)	0.61 (0.20–1.84)	0.41
Myocardial infarction				
Q-wave myocardial infarction	11 (2.6%)	8 (1.9%)	0.71 (0.29–1.74)	0.49
Non–Q-wave myocardial infarction	7 (1.7%)	7 (1.6%)	0.97 (0.34–2.74)	1.00
Revascularization*	64 (15.4%)	50 (11.6%)	0.76 (0.54–1.07)	0.13
Target lesion revascularization†	33 (7.9%)	35 (8.1%)	1.03 (0.65–1.62)	1.00
Non-target lesion revascularization	31 (7.4%)	15 (3.5%)	0.47 (0.26–0.86)	0.01
Coronary bypass graft	10 (2.4%)	7 (1.6%)	0.68 (0.26–1.77)	0.47
PCI	54 (13.0%)	43 (10.0%)	0.77 (0.53–1.13)	0.20

*Both surgical and percutaneous, excluding repeat interventions due to restenosis during the first 6 months of follow-up.

†Revascularizations due to restenosis within the segment treated at index procedure ± 5 mm proximal and distal segments.

effects on the underlying atherosclerotic disease. It is well known that statins slow the progression of atherosclerosis by reducing total and LDL cholesterol levels. Recently, new concepts have emerged with the description of "pleiotropic" effects of statins[12] such as decreased vascular inflammation,[13] improved endothelial function,[14] and decreased platelet aggregation and thrombogenesis.[15] It is worth noting that the anti-inflammatory properties of statins have been shown to decrease the detrimental influence of inflammation on coronary risk.[16]

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