Fluvastatin for Prevention of Cardiac Events Following Successful First Percutaneous Coronary Intervention

A Randomized Controlled Trial

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Context Percutaneous coronary intervention (PCI) is associated with excellent short-term improvements in ischemic symptoms, yet only three fifths of PCI patients at 5 years and one third of patients at 10 years remain free of major adverse cardiac events (MACE).

Objective To determine whether treatment with fluvastatin reduces MACE in patients who have undergone PCI.

Design and Setting Randomized, double-blind, placebo-controlled trial conducted at 77 referral centers in Europe, Canada, and Brazil.

Patients A total of 1677 patients (aged 18-80 years) recruited between April 1996 and October 1998 with stable or unstable angina or silent ischemia following successful completion of their first PCI who had baseline total cholesterol levels between 135 and 270 mg/dL (3.5-7.0 mmol/L), with fasting triglyceride levels of less than 400 mg/dL (4.5 mmol/L).

Interventions Patients were randomly assigned to receive treatment with fluvastatin, 80 mg/d (n = 844), or matching placebo (n = 833) at hospital discharge for 3 to 4 years.

Main Outcome Measure Survival time free of MACE, defined as cardiac death, nonfatal myocardial infarction, or reintervention procedure, compared between the treatment and placebo groups.

Results Median time between PCI and first dose of study medication was 2.0 days, and median follow-up was 3.9 years. MACE-free survival time was significantly longer in the fluvastatin group ($P = .01$). One hundred eighty-one (21.4%) of 844 patients in the fluvastatin group and 222 (26.7%) of 833 patients in the placebo group had at least 1 MACE (relative risk [RR], 0.78; 95% confidence interval [CI], 0.64-0.95; $P = .01$). This result was independent of baseline total cholesterol levels (above [RR, 0.76; 95% CI, 0.56-1.04] vs below [RR, 0.77; 95% CI, 0.57-1.02] the median). In subgroup analysis, the risk of MACE was reduced in patients with diabetes (n = 202; RR, 0.53; 95% CI, 0.29-0.97; $P = .04$) and in those with multivessel disease (n = 614; RR, 0.66; 95% CI, 0.48-0.91; $P = .01$) who received fluvastatin compared with those who received placebo. There were no instances of creatine phosphokinase elevations 10 or more times the upper limit of normal or rhabdomyolysis in the fluvastatin group.

Conclusion Fluvastatin treatment in patients with average cholesterol levels undergoing their first successful PCI significantly reduces the risk of major adverse cardiac events.

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PERCUTANEOUS CORONARY INTERvention (PCI) comprises a group of procedures that are used to relieve ischemic symptoms due to coronary atherosclerotic narrowing in patients with increasingly earlier stages of coronary heart disease (CHD). The most frequently performed PCI procedure is balloon angioplasty with or without stenting. In the United States, balloon angioplasty procedures increased nearly 4-fold between 1987 and 1999, and in 1999, 1.1 million angioplasty procedures, both with and without stent placement, were performed in the United States alone.[1]

Percutaneous coronary intervention has been demonstrated to be at least as effective as coronary artery bypass grafting (CABG) in terms of survival and prevention of myocardial infarction (MI) in appropriately selected patients with either single-vessel or multivessel disease.[2,3] Although PCI achieves short-term improvements in ischemic

For editorial comment see p 3259.

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symptoms in 9 of 10 patients who undergo the procedure, patients continue to have high rates of postprocedure cardiovascular events. Approximately 3 of 5 patients at 5 years and only 1 of 3 patients at 10 years remain free of major adverse cardiac events (MACE).[4]

Lipid-lowering treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been shown to significantly reduce the incidence of cardiovascular events in patients with CHD[5-8] but not to reduce the 6-month restenosis rate after PCI.[9-11] Data supporting the benefit of these treatments following PCI are currently limited to retrospective analyses and to patients at relatively advanced stages of cardiac disease, with average or high pretreatment cholesterol values, and with statin treatment initiated 6 months or later following PCI.

Until recently, lipid-lowering treatment with statins was a neglected therapeutic approach in patients undergoing PCI. In a European study assessing the relation between serum cholesterol and long-term restenosis following coronary angioplasty in 2753 patients, only 9.7% of patients with total cholesterol levels of less than 301 mg/dL (7.8 mmol/L) and 17.2% of those with a level of 301 mg/dL (7.8 mmol/L) or greater were receiving lipid-lowering treatment at trial entry. Less than 25% were taking lipid-lowering drugs at 6-month follow-up.[12] In a recently published survey conducted in 1 center in the United States,[13] only 26.5% of 5052 patients undergoing PCI between 1993 and 1999 were receiving statin treatment at the time of the procedure.

The Lescol Intervention Prevention Study (LIPS) was designed to investigate whether cholesterol lowering with fluvastatin, initiated within days following successful completion of first PCI (with or without stenting), would prolong cardiac disease–free survival time compared with placebo.

METHODS

Study Design

A detailed description of the study design of LIPS has been reported.[14] The study was a double-blind, randomized placebo-controlled trial. Men and women aged 18 to 80 years were recruited from 57 interventional centers in 10 countries (Belgium, France, Germany, Italy, United Kingdom, the Netherlands, Spain, Switzerland, Canada, and Brazil). All patients had successfully undergone their first PCI (index procedure) of 1 or more lesions in the native coronary arteries. Successful PCI was defined as a reduction of the stenosis diameter to less than 50% in the target lesion without evidence of myocardial necrosis, need for repeat PCI or CABG, or death before hospital discharge. Any type of PCI was allowed and included balloon angioplasty with or without stent placement, rotational or directional atherectomy, laser ablation, transluminal extraction catheter, or cutting balloon. The procedure was performed during 1 hospital stay at one of the 57 recruiting interventional centers, and patients were followed up after hospital discharge at the same clinic or at a referral center, with a total of 77 sites participating in the study.

Patients were eligible for enrollment in the study if they had a total cholesterol level between 135 and 270 mg/dL (3.5-7.0 mmol/L), with fasting triglyceride levels of less than 400 mg/dL (4.5 mmol/L) before the index procedure. The upper total cholesterol limit for eligibility was 212 mg/dL (5.5 mmol/L) for patients whose baseline lipids were measured from blood drawn 24 hours to 4 weeks following MI and 232 mg/dL (6.0 mmol/L) for patients with type 1 or 2 diabetes mellitus. Exclusion criteria included sustained systolic blood pressure of more than 180 mm Hg and diastolic blood pressure of more than 100 mm Hg despite medical therapy, left ventricular ejection fraction of less than 30%, a history of previous PCI or CABG, severe valvular disease, idiopathic cardiomyopathy or congenital heart disease, severe renal dysfunction (defined as serum creatinine level >1.8 mg/dL [160 µmol/L]), obesity (defined as a body mass index >35 kg/m^2), and the presence of malignant or other disease with a life expectancy of less than 4 years. All patients provided written informed consent, and the ethics committee at each participating center approved the trial.

Treatment

After inclusion, patients were randomly assigned to receive either fluvastatin, 40 mg twice per day (Lescol, Novartis Pharma AG, Basel, Switzerland) or matching placebo for a period of at least 3 years and no longer than 4 years. Patients were to be allocated to treatment in the order in which they were enrolled into the study at each center according to medication pack numbers using block randomization, with each interventional center receiving multiple blocks. All patients received dietary and lifestyle counseling at hospital discharge. Investigators remained blinded to all lipid values unless total cholesterol exceeded 278 mg/dL (7.2 mmol/L); in that case, the central laboratory informed the appropriate clinical investigators. If the total cholesterol level remained higher than 278 mg/dL (7.2 mmol/L) for 3 months or more, patients were to discontinue study medication at the discretion of the study investigator and receive an open-label statin or other lipid-lowering therapy. Investigators were requested not to perform any determination of serum lipid levels in the local laboratory during the course of the study. The protocol did not restrict or specify any other diagnostic or therapeutic measures except as indicated in the exclusion criteria.

Patients were assessed at the referral trial centers at week 6 after randomization and every 6 months thereafter. All attempts were made to retain patients in the study regardless of trial medication intake.

Laboratory measures, including serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting triglyceride levels, were assessed at a central laboratory (Analytico Medinet, Breda, the Netherlands) from fasting blood samples.

Outcomes

The primary clinical composite end point was development of a MACE, defined as cardiac death (any death unless an unequivocal noncardiac cause could be established); nonfatal MI (appearance of pathological Q waves that were absent at baseline or a total creatine kinase level >2 times the upper limit of normal [ULN] with presence of CK isoenzyme MB higher than the ULN); or a reintervention procedure (CABG, repeat PCI, or PCI for a new lesion). Angiographic assessments without interventions were not included.

Prespecified secondary clinical end points were MACE, excluding reintervention procedures (surgical or PCI) occurring in the first 6 months of follow-up for lesions treated at the index procedure, cardiac mortality, noncardiac mortality, all-cause mortality, combined cardiac mortality and MI, and combined all-cause mortality and MI. Secondary end points also included treatment effects on measured lipid levels throughout the trial, as well as the safety and tolerability of fluvastatin.

An independent critical events committee blinded to treatment assignment reviewed all deaths and suspected nonfatal MIs for adjudication, and all analyses were based on the committee's classification of the end points.

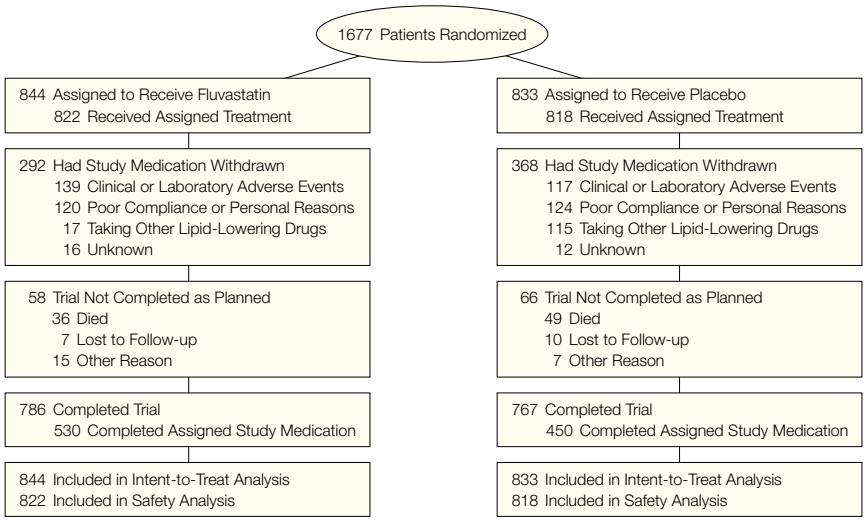
Statistical Analysis

All analyses of the primary and secondary end points were performed with results stratified by treatment center. All randomized patients constituted the intent-to-treat population. This was the primary efficacy analysis population and was used for both the primary end-point and secondary end-point analyses. All patients were analyzed according to their original treatment allocation. All primary and secondary end-point data were collected for the entire duration of the follow-up for all patients, whether or not they were receiving study medication or other lipid-lowering treatments, and were used in the statistical analyses. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. The log-rank test was used for the primary end point, and Kaplan-Meier curves were used to examine MACE-free survival time. The Cox proportional hazards model and the Cochran-Mantel-Haenszel test were used to assess risk reduction and to compare the incidences of the primary and secondary clinical end points, respectively.

Study sample size was calculated to provide the study with 90% power for a 2-sided α-level of .05, assuming a 25% MACE rate at 3 years in the placebo group and an 18.75% MACE rate in the fluvastatin group. Because age (≥65 vs <65 years), multivessel vs single-vessel disease, previous MI, ejection fraction (below vs above median), high total cholesterol levels (above vs below median), and diabetes are known risk factors that may have an impact on the primary clinical end point, a Cox regression analysis was performed on the primary end point using these factors as covariates.

Two interim analyses were conducted using the O'Brien-Fleming stopping rule by an independent data safety and monitoring board at 1 and 2 years following recruitment of the last patient. These analyses were aimed at ensuring adherence to the study protocol, assessing the appropriateness of sample size and statistical assumptions, and considering ethical issues that could have affected the continuation of the study. Consequently, the significance level for the primary analysis was adjusted to .04592. All secondary end points were tested using a .05 level of significance. All data were analyzed using SAS software, version 6.12 (SAS Institute Inc, Cary, NC).

Figure 1. Flow of Participants Through the Trial



The number of patients screened was not determined. Follow-up information was sought for all patients who were withdrawn early from the study. All eligible patients were randomized.

RESULTS

Patients

Between April 1996 and October 1998, a total of 1677 patients were recruited and were randomly assigned to receive either fluvastatin (n = 844) or placebo (n = 833) (FIGURE 1). The groups were well balanced with regard to baseline characteristics, except for a significant between-group difference in the incidence of diabetes mellitus (14.2% vs 9.8% for the fluvastatin and placebo groups, respectively; 95% confidence interval [CI] of the difference between groups, 1.3-7.5) (TABLE 1). Balloon angioplasty with or without stent placement was performed in 98% of patients. The mean time between index

PCI and randomization was 2.7 days in both groups (median, 2.0 days; range, 0-22 days in the fluvastatin group and 0-21 days in the placebo group). Median time from index PCI to initiation of study medication was 2.0 days. Median follow-up was 3.9 years in both groups.

Until the time of the first MACE or up to completion of follow-up for patients without MACE, 19.3% of the patients in the fluvastatin group were taking less than 80% of the study treatment regimen while not taking other lipid-lowering drugs. On the other hand, 10.7% of patients in the fluvastatin group and 24% of patients in the placebo group were taking other lipid-lowering drugs (primarily statins).

Table 1. Baseline Patient Characteristics*

	Fluvastatin (n = 844)	Placebo (n = 833)
Male sex, No. (%)	711 (84.2)	695 (83.4)
Age, y	60.0 (10.1)	60.0 (9.8)
Ejection fraction, %	62.2 (12.0)	61.8 (12.0)
Systolic BP, mm Hg	128.1 (18.2)	128.4 (18.4)
Diastolic BP, mm Hg	75.1 (10.3)	75.6 (10.3)
BMI, kg/m^2	26.7 (3.3)	26.4 (3.3)
Indication for PCI, No. (%)		
Unstable angina	417 (49.4)	407 (48.9)
Stable angina	346 (41.0)	325 (39.0)
Silent ischemia	72 (8.5)	91 (10.9)
Multivessel disease	322 (38.2)	292 (35.1)
Type of PCI, No. (%)		
Balloon only	287 (34.0)	295 (35.4)
Stent	540 (64.0)	515 (61.8)
Perfusion balloon	18 (2.1)	19 (2.3)
Rotational ablation	7 (0.8)	7 (0.8)
Directional atherectomy	5 (0.6)	4 (0.5)
Excimer laser	3 (0.4)	5 (0.6)
Stent implanted, No./total (%) of lesions	639/1141 (56.0)	598/1083 (55.2)
Risk factors, No. (%)		
Previous MI	371 (44.0)	373 (44.8)
Diabetes mellitus†	120 (14.2)	82 (9.8)
History of hypertension	330 (39.1)	317 (38.1)
History of stroke	17 (2.0)	27 (3.2)
Peripheral vascular disease	50 (5.9)	57 (6.8)
Smoking status		
Never	240 (28.4)	238 (28.6)
Previous	393 (46.6)	360 (43.2)
Current	211 (25.0)	235 (28.2)
Family history of CHD	239 (28.3)	251 (30.1)
Concomitant medications, No. (%)		
Aspirin	822 (97.4)	815 (97.8)
β-Blockers	584 (69.2)	591 (70.9)
Calcium antagonists	496 (58.8)	469 (56.2)
Nitrates	462 (54.7)	468 (56.2)
ACE inhibitors	321 (38.0)	317 (38.1)
Diuretics	167 (19.8)	159 (19.1)
Lipids, mg/dL [mmol/L]		
Total cholesterol	200 (30.9) [5.2 (0.8)]	199 (329) [5.2 (0.9)]
LDL-C	131 (29.0) [3.4 (0.8)]	132 (30.5) [3.4 (0.8)]
HDL-C	38 (12.0) [1.0 (0.3)]	37 (11.6) [1.0 (0.3)]
Triglycerides	160 (70.8) [1.8 (0.8)]	160 (61.9) [1.7 (0.7)]

*Data are expressed as mean (SD) unless otherwise specified. BP indicates blood pressure; BMI, body mass index; PCI, percutaneous coronary intervention; MI, myocardial infarction; CHD, coronary heart disease; ACE, angiotensin-converting enzyme; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.
†Significant between-group difference at baseline (odds ratio, 4.4%; 95% confidence interval, 1.3-7.5).

Concurrent Medication

During the study, 97% of patients in the fluvastatin group and 98% in the placebo group were taking aspirin. The proportion of patients taking other cardiovascular drugs during the study, such as β-blockers, calcium antagonists, nitrates, angiotensin-converting enzyme inhibitors, and diuretics, was similar between groups (Table 1).

Primary End Point

During the follow-up period, MACE-free survival time was significantly longer in the fluvastatin group (first quartile of time to first MACE, 1558 days; 95% lower confidence bound, 1470 days) compared with the placebo group (1227 days; 95% lower confidence bound, 858 days; $P = .01$). For the primary end point, the Kaplan-Meier curves for the fluvastatin and placebo groups begin to separate at approximately 1.5 years and continue to diverge up to study termination (FIGURE 2). One hundred eighty-one (21.4%) of the 844 patients in the fluvastatin group and 222 (26.7%) of the 833 placebo controls had at least 1 MACE, resulting in a statistically significant reduction in risk of MACE for fluvastatin compared with placebo (relative risk [RR], 0.78; 95% CI, 0.64-0.95; $P = .01$ by the Cox proportional hazards model) (TABLE 2) and a significant relative reduction of 20% ($P = .006$ by the Cochran-Mantel-Haenszel test) (Table 2). During the follow-up period, 13 patients in the fluvastatin group (1.5%) and 24 placebo controls (2.9%) died from cardiac causes, 30 patients in the fluvastatin group (3.6%) and 38 placebo controls (4.6%) had a nonfatal MI, and 167 in the fluvastatin group (19.8%) compared with 193 placebo controls (23.2%) underwent CABG or PCI.

Secondary End Points

The Cox regression analysis performed on the primary end point us-

ing predefined risk factors as covariates revealed significant effects for multivessel vs single-vessel disease and presence vs absence of diabetes at baseline. The risk of MACE was lower in the subgroup of patients with multivessel disease (23% vs 33.9%; RR, 0.66; 95% CI, 0.48-0.91; $P = .01$) and lower in the subgroup of patients with diabetes (21.7% vs 37.8%; RR, 0.53; 95% CI, 0.29-0.97; $P = .04$) in the fluvastatin group compared with the placebo group (TABLE 3). The risk of MACE among those with baseline cholesterol levels below the group median (200 mg/dL [5.2 mmol/L]; interquartile range, 162.4-189.5 mg/dL [4.2-4.9 mmol/L]) was 20.9% for those taking fluvastatin and 25.3% for those receiving placebo (RR, 0.77; 95% CI, 0.57-1.02) whereas for those with baseline levels above the group median (200 mg/dL [5.2 mmol/L]; interquartile range, 208.8-235.9 mg/dL [5.4-6.1 mmol/L]), the risk of MACE was 20.5% for fluvastatin and 27.5% for placebo (RR, 0.76; 95% CI, 0.56-1.04).

The primary end point was assessed in men and women in a subset analysis. The risk reduction achieved in the fluvastatin group was similar in both groups (for men, RR, 0.79; 95% CI, 0.64-0.98 and for women, RR, 0.66; 95% CI, 0.38-1.14) but was statistically significant only for the subgroup of men ($P = .03$), which represents 84% of the total study population.

Other subgroups of interest were assessed in a post hoc analysis by anginal status or type of PCI treatment (ie, balloon angioplasty or stenting), the latter excluding reinterventions (surgical or PCI) occurring in the first 6 months of follow-up and indicated to treat a lesion dilated at index procedure. The risk reduction in MACE achieved with fluvastatin treatment in these subgroups was similar to that observed in the overall study population and other subgroups (Table 3).

When the MACE-free survival time was assessed, excluding reintervention procedures (surgical or PCI) occurring in the first 6 months of follow-up for lesions treated at the index procedure, the fluvastatin group and placebo group curves were observed to separate earlier than in the primary analysis, at approximately 6 months, and showed a significantly extended MACE-free survival time in the fluvastatin group ($P<.001$) (FIGURE 3). The risk of MACE was 33% lower (RR, 0.67; 95% CI, 0.54-0.84; $P<.001$) in the fluvastatin group than in placebo controls in this analysis (Table 2).

There was also a nonsignificant trend favoring the fluvastatin group for reduction of the end points of cardiac death and combined cardiac death and nonfatal MI (Table 2).

Lipoprotein Levels

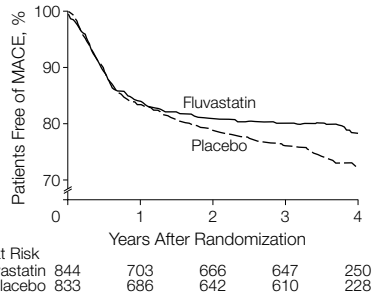
By 6 weeks, fluvastatin significantly reduced LDL-C (median reduction, 27%; 95% CI, 25%-29%) compared with placebo (median increase, 11%; 95% CI, 9%-13%), and these effects continued throughout follow-up (FIGURE 4). Fasting triglyceride levels followed a different pattern, with greater median reductions in the fluvastatin group than in the placebo group observed as early as 6 weeks (–14%; 95% CI, –13% to –18% vs 0%; 95% CI, 0%-4%) and maintained until approximately 2.5 years of follow-up (–22%; 95% CI, –18% to –25% vs –14%; 95% CI, –9% to –17%). At study end, however, the median reduction in fasting triglycerides was 14% in both groups. Levels of HDL-C increased by a median of 22% in both groups.

Safety

The population available for safety analysis included 822 patients in the fluvastatin group and 818 placebo controls. One hundred seventy-four patients (21.2%) in the fluvastatin group temporarily or permanently discontinued study medication due to adverse events compared with 196 patients (24.0%) in the placebo group. Twenty-three patients in the fluvastatin group (2.7%) and 25 in the placebo group (3.0%) died from noncardiac causes (TABLE 4).

There were no elevations in creatine kinase levels of 10 times the ULN or more in the fluvastatin group, and there were 3 reported cases in the pla-

Figure 2. MACE-Free Survival Time



MACE indicates major adverse cardiac events. $P = .01$ by log-rank test.

Table 2. Incidence and Risk of Primary and Secondary Outcome End Points in the Intent-to-Treat Population*

	Incidence, No. (%)			Fluvastatin vs Placebo	
	Fluvastatin (n = 844)	Placebo (n = 833)	*P* Value†	RR (95% CI)	*P* Value‡
MACE (primary outcome)	181 (21.4)	222 (26.7)	.006	0.78 (0.64-0.95)	.01
Secondary outcomes					
Cardiac death	13 (1.5)	24 (2.9)	.06	0.53 (0.27-1.05)	.07
Noncardiac death	23 (2.7)	25 (3.0)	.65	0.84 (0.48-1.49)	.56
All-cause death	36 (4.3)	49 (5.9)	.11	0.69 (0.45-1.07)	.10
Cardiac death/MI	42 (5.0)	60 (7.2)	.05	0.69 (0.46-1.02)	.07
All-cause death/MI	65 (7.7)	84 (10.1)	.07	0.75 (0.54-1.03)	.08
MACE other than restenosis§	135 (16.0)	187 (22.5)	<.001	0.67 (0.54-0.84)	<.001

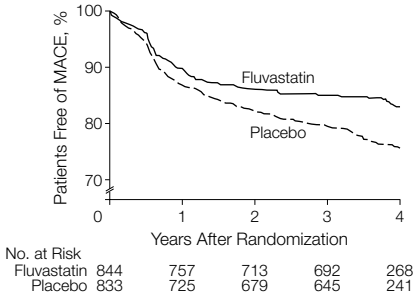
*RR indicates relative risk; CI, confidence interval; and MACE, major adverse cardiac event (composite end point of cardiac death, nonfatal myocardial infarction [MI], or reintervention procedure).
†By Cochran-Mantel-Haenszel test.
‡Based on Cox proportional hazards model.
§MACE excluding reinterventions (surgical or percutaneous coronary reintervention) occurring in the first 6 months of follow-up for lesions treated at the index procedure.

Table 3. Incidence and Risk of MACE in Subpopulations of the Intent-to-Treat Population*

	Incidence, No./Total (%)			Fluvastatin vs Placebo	
	Fluvastatin (n = 844)	Placebo (n = 833)	*P* Value†	RR (95% CI)	*P* Value‡
Single-vessel disease	107/522 (20.5)	123/541 (22.7)	.17	0.86 (0.66-1.13)	.28
Multivessel disease	74/322 (23.0)	99/292 (33.9)	.008	0.66 (0.48-0.91)	.01
Nondiabetic	155/724 (21.4)	191/751 (25.4)	.05	0.83 (0.67-1.03)	.10
Diabetic	26/120 (21.7)	31/82 (37.8)	.02	0.53 (0.29-0.97)	.04
No prior MI	108/473 (22.8)	129/460 (28.0)	.047	0.79 (0.61-1.03)	.08
Prior MI	73/371 (19.7)	93/373 (24.9)	.046	0.77 (0.57-1.06)	.11
Stable angina§	93/418 (22.3)	109/416 (26.2)	.12	0.80 (0.60-1.07)	.13
Unstable angina	87/417 (20.9)	111/407 (27.3)	.01	0.72 (0.54-0.96)	.03
Balloon PCI‖	44/287 (15.3)	68/295 (23.1)	.002	0.57 (0.38-0.84)	.004
Stent PCI‖	90/540 (16.7)	114/515 (22.1)	.02	0.71 (0.54-0.94)	.02
Total cholesterol below median¶	88/420 (20.9)	109/430 (25.3)	.06	0.77 (0.57-1.02)	.07
Total cholesterol above median#	74/361 (20.5)	95/346 (27.5)	.049	0.76 (0.56-1.04)	.09
LDL-C below median**	85/399 (21.3)	108/406 (26.6)	.03	0.74 (0.55-0.97)	.047
LDL-C above median††	76/375 (20.3)	92/359 (25.6)	.15	0.80 (0.58-1.09)	.17

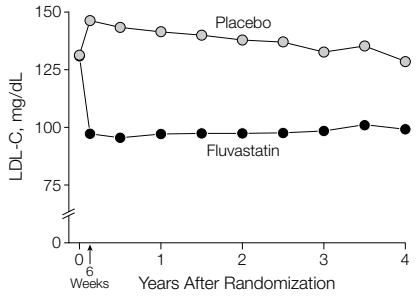
*MACE indicates major adverse cardiac events; RR, relative risk; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; and LDL-C, low-density lipoprotein cholesterol.
†By Cochran-Mantel-Haenszel test.
‡Based on Cox proportional hazards model.
§Including patients with silent ischemia.
‖Excluding reinterventions (surgical or PCI) occurring in the first 6 months of follow-up for lesions treated at the index procedure.
¶Baseline median value, 200 mg/dL (5.2 mmol/L); mean value, 178 mg/dL (4.6 mmol/L).
#Baseline median value, 200 mg/dL (5.2 mmol/L); mean value, 228 mg/dL (5.9 mmol/L).
**Baseline median value, 132 mg/dL (3.4 mmol/L); mean value, 108 mg/dL (2.8 mmol/L).
††Baseline median value, 132 mg/dL (3.4 mmol/L); mean value, 159 mg/dL (4.1 mmol/L).

Figure 3. MACE-Free Survival Time Excluding Reinterventions



Data were calculated excluding surgical or percutaneous coronary reinterventions occurring in the first 6 months of follow-up for lesions treated at the index procedure. MACE indicates major adverse cardiac events. $P<.001$ by log-rank test.

Figure 4. Change in LDL-C Levels From Baseline Throughout Follow-up



LDL-C indicates low-density lipoprotein cholesterol. To convert LDL-C to mmol/L, multiply by 0.0259. $P<.001$ for fluvastatin vs placebo for the entire duration of the study, based on analysis of variance with treatment and visit as factors, using SAS PROC GLM.

cebo group. No rhabdomyolysis was reported in patients treated with fluvastatin during the study. Ten patients (1.2%) in the fluvastatin group and 3 (0.4%) in the placebo group had persistent, clinically relevant elevations in aspartate aminotransferase or alanine aminotransferase levels, defined as levels of at least 3 times the ULN on 2 consecutive occasions. Cancers were reported in 95 patients during the study: 46 in the fluvastatin group and 49 in the placebo group.

COMMENT

Secondary prevention investigations have shown that statins can decrease the incidence of both fatal and nonfatal coronary events.[5-8] However, these studies generally enrolled patients with relatively advanced cardiac disease. In addition, as few as 8% and up to only one third of patients enrolled in earlier trials had previously received PCI, and in these patients, statin therapy was initiated 6 months or more after the intervention. Only the Cholesterol and Recurrent Events (CARE) trial included a sufficient number of post-PCI patients to show a significant reduction in ischemic events in a retrospective analysis.[15] In contrast, our study is the first prospective trial in patients undergoing their first PCI with clinical outcomes as the primary end point. Patients enrolled in our study generally had an earlier CHD stage (all had unstable or stable angina or silent ischemia, and less than half had prior MI) and statin therapy was initiated very early after the index procedure compared with earlier trials.

Results of the LIPS study show that in patients with average cholesterol levels, early cholesterol-lowering treatment with fluvastatin, 80 mg/d, following first PCI with or without stenting resulted in a 5.3% absolute reduction and a 22% relative reduction in the risk of fatal or nonfatal major adverse cardiac events during 4 years of follow-up compared with placebo. These results suggest that treating 19 post-PCI patients with fluvastatin for 4 years would prevent 1 fatal or nonfatal MACE (number needed to treat, 19; 95% CI, 11-82), suggesting benefit similar to that observed in other secondary prevention trials.[5-8] This risk reduction may have been even larger, considering that ultimately, 24% of patients in the placebo group were taking other lipid-lowering treatment compared with 10.7% in the fluvastatin group, and that 19.3% of patients in the fluvastatin group were not compliant with the treatment regimen. These noncompliance figures are similar to those reported in a recently published statin secondary prevention trial.[8] The crossover rate to active medication in the placebo group that was observed in these trials suggests the need to reconsider

the clinical and ethical aspects of investigations that assess the benefits of cholesterol-lowering medications vs placebo.

The subgroup analyses showing benefit of therapy in multivessel disease and in diabetic patients are not surprising because these factors are known to increase CHD risk.[4,16,17] In these subpopulations, fluvastatin treatment appears to stabilize CHD risk, with an incidence of cardiac events in patients taking fluvastatin similar to that observed in the subgroups of patients with single-vessel disease and nondiabetic patients.

Previous large, randomized studies indicated that statin therapy does not prevent restenosis as assessed by quantitative angiography at 6 months.[9-11] The recent Fluvastatin Angiographic Restenosis (FLARE) study[11] showed a significantly lower incidence of total death and MI with fluvastatin, 80 mg/d, at 40 weeks after PCI (1.4% vs 4.0%; $P = .03$), although the composite clinical end point that included CABG and PCI was not significantly different from placebo controls. In view of these findings, the MACE end point in LIPS was assessed in a prespecified analysis excluding reinterventions (surgical or PCI) in the first 6 months of follow-up for lesions treated at the index PCI. In this analysis, separation of the fluvastatin MACE-free survival curve from the placebo control curve occurred at approximately 6 months, earlier than in the primary analysis, and risk reduction was greater. This suggests that earlier benefits can be observed in post-PCI patients with fluvastatin therapy when overlapping restenotic complications are not taken into account.

The cholesterol level distribution observed in LIPS patients is representative of that of an unselected patient population undergoing PCI.[9] In LIPS, the benefits associated with fluvastatin, 80 mg/d, on lipid levels and clinical outcomes were demonstrated in a population with a mean baseline LDL-C value of 132 mg/dL (3.4 mmol/L) (range, 42-243 mg/dL [1.1-6.3 mmol/L]). The mean baseline LDL-C level found in LIPS is in the lowest range of those reported in 4 previous major long-term secondary prevention statin outcomes trials.[5-8] Of these trials, only CARE and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial suggest that the benefit of lipid lowering with a statin is diminished in patients with baseline LDL-C values of less than 130 mg/dL (3.4 mmol/L) recommended for initiation of drug therapy.[7,18] In contrast, LIPS and the Heart Protection Study[8] suggest that the benefit is significant and equal regardless of baseline cholesterol strata.

While elevated blood cholesterol levels are a well-established independent risk factor for the development of cardiovascular disease, there has been ongoing debate regarding the value of cholesterol lowering and the optimal time for initiation of drug therapy in patients with normal or low LDL-C levels (<130 mg/dL [3.4 mmol/L]). These 2 most recent studies suggest that the decision to initiate cholesterol-lowering therapy should be based on risk assessment and not on baseline cholesterol levels. The results of LIPS are consistent with the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults guidelines, which recommend the reduction of LDL-C to less than 100 mg/dL (2.6 mmol/L) in patients with CHD or CHD risk equivalents.[19]

The shift to a more aggressive approach to lipid lowering comes at a time when the typical PCI patient profile is evolving from the patient with chronic angina to the patient experiencing his or her first anginal episode.[20,21] In these patients, a more aggressive interventional approach has been advocated.[22,23] This trend toward treatment earlier in the history of angina has, in part, fueled the dramatic growth (nearly 4-fold) in balloon angioplasty procedures performed in the United States from 1987 to 1999.[1] While initial evidence has shown that drug-eluting stents may help reduce stent failure due to restenosis,[24,25] the results of LIPS demonstrate that early postprocedure statin use reduces the rate of fatal and nonfatal cardiac events related to progression of the underlying disease. Thus, a combined approach of mechanical treatment and metabolic secondary prevention involving initiation of cholesterol-lowering treatment with a statin at the time of first PCI may be an effective strategy.

Table 4. Causes of Noncardiac Mortality

	No. of Patients	
	Fluvastatin (n = 844)	Placebo (n = 833)
Cancer	14	18
Gastrointestinal	2	6
Pulmonary	5	3
Prostate	2	2
Pancreas	2	1
Cerebral	0	3
Other	3	3
Respiratory failure	3	2
Sepsis	1	3
Stroke	2	1
Other	3	1
Total No. (%)	**23** (2.7)	**25** (3.0)

Because of the need for long-term treatment with lipid-lowering drugs, the safety of the drug used is of paramount importance. In our study, no cases of creatine kinase elevations to more than 10 times the ULN and no severe muscular toxic effects were observed with fluvastatin at a dosage of 80 mg/d, and other adverse effects were reported with similar frequency in the fluvastatin and placebo groups.

In conclusion, LIPS is the first prospective trial to demonstrate a significant risk reduction in fatal or nonfatal MACE as a result of statin therapy with fluvastatin, 80 mg/d, initiated early following successful completion of first PCI, with or without stenting. The results of LIPS support the use of early lipid-lowering therapy with fluvastatin in post-PCI patients, regardless of baseline lipid level.

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Role of the Sponsor: The study was centrally coordinated by a clinical trial manager (Marie-Odile Freudenreich, RN) at Novartis Pharma AG and monitored by Novartis country monitors. Data entry and management were performed at Cardialysis BV, Rotterdam, the Netherlands, and coordinated by Cardialysis study personnel (Peter-Paul Kint, study manager). Clemens Disco, MSc, performed statistical analyses at Cardialysis. Cardialysis is an independent clinical research organization specializing in cardiology with a network of more than 1200 cardiology sites worldwide. Cardialysis is affiliated with the Thoraxcenter of the Erasmus University Hospital in Rotterdam. A Novartis trial statistician (John O. Logan, MSc) and a medical data manager (Graham Craig) were also involved in the statistical analyses and data management in collaboration with Cardialysis study personnel. Their main role included validation of the report outputs and ensuring data quality. The study database is available at both Cardialysis and Novartis. The study was supervised by a steering committee chaired by Dr Serruys and cochaired by Dr de Feyter. The steering committee included 1 member from each participating country and 1 medical representative of Novartis. The authors were fully involved in the review and discussion of the data and drafts of the manuscript until finalization. Two experts in cardiology and dyslipidemia (Michael Davidson, MD, and Anders Olsson, MD) were involved in critical review and intellectual discussion of the data, independent of the conduct of the study. Cardialysis and Novartis personnel provided administrative, technical, and material support during preparation of the manuscript.

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