Long-Term *Fluvastatin* Reduces the Hazardous Effect of Renal Impairment on Four-Year Atherosclerotic Outcomes (a LIPS Substudy)

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Mild renal impairment is an important risk factor for late cardiovascular complications. This substudy of the Lescol Intervention Prevention Study (LIPS) assessed the effect of fluvastatin on outcome of patients who had renal dysfunction and those who did not. Complete data for creatinine clearance calculation (Cockcroft-Gault formula) were available for 1,558 patients (92.9% of the LIPS population). Patients were randomized to fluvastatin or placebo after successful completion of a first percutaneous coronary intervention. Follow-up time was 3 to 4 years. The effect of baseline creatinine clearance on coronary atherosclerotic events (cardiac death, nonfatal myocardial infarction, and coronary reinterventions not related to restenosis) was evaluated. Baseline creatinine clearance (logarithmic transformation) was inversely associated with an incidence of adverse events among patients who received placebo (hazard ratio 0.99, 95% confidence interval 0.982 to 0.998, p = 0.01). However, no association was noted between creatinine clearance and the incidence of adverse events among patients who received fluvastatin (hazard ratio 1.0, 95% confidence interval 0.99 to 1.0, p = 0.63). No further deterioration in creatinine clearance was observed during follow-up, regardless of baseline renal function or allocated treatment. Occurrence of adverse events was not related to changes in renal function during follow-up. Fluvastatin therapy markedly decreased the risk of coronary atherosclerotic events after percutaneous intervention in patients who had lower values of creatinine clearance at baseline. The benefit of fluvastatin was unrelated to any effect on renal function.

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In the recent Lescol Intervention Prevention Study (LIPS), long-term therapy with fluvastatin decreased the incidence of cardiac events in patients who underwent percutaneous coronary intervention.[1] The present study analyzed the results of LIPS to investigate (1) the effect of baseline renal function on occurrence of long-term adverse events, (2) whether therapy with fluvastatin decreased the expected hazardous effect of renal impairment, (3) the effect of fluvastatin on renal function during follow-up, and (4) the relation between changes in renal function over time and the occurrence of adverse events.

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METHODS

Study design and patient population: The study design and primary results of LIPS have been described elsewhere.[1] Briefly, after a first successful percutaneous coronary intervention (residual stenosis <50%, absence of postprocedural in-hospital myocardial necrosis, repeat revascularization, or death), patients were randomized to receive fluvastatin therapy (Lescol, Novartis Pharma AG, Basel, Switzerland; 40 mg 2 times daily) or placebo for 3 to 4 years.

At enrollment, patients had to fulfill ≥1 of the following lipid profile criteria: (1) total cholesterol level of 135 to 270 mg/dl with a fasting triglyceride level <400 mg/dl, (2) total cholesterol level <212 mg/dl for patients whose lipids levels were measured 24 hours to 4 weeks after an episode of myocardial infarction, or (3) total cholesterol level <232 mg/dl for patients who had diabetes mellitus. Exclusion criteria included a baseline serum creatinine value >1.8 mg/dl. The study protocol was approved by the local ethics committees, and all patients gave informed written consent.

Lipoproteins and evaluation of renal function: Each patient was clinically evaluated ≥8 times after randomization. Blood lipid levels were measured at all visits, and serum creatinine was measured at baseline

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TABLE 1 Baseline Patient Characteristics According to Renal Function

	Normal Renal Function (n = 1,248)	Mild Renal Impairment (n = 310)	p Value
Age (yrs)	58 ± 9	69 ± 7	<0.01
Women	146 (12)	102 (33)	<0.01
Height (cm)	170 ± 8	165 ± 8	<0.01
Weight (kg)	79 ± 11	68 ± 10	<0.01
Systolic blood pressure (mm Hg)	127 ± 18	132 ± 20	<0.01
Diastolic blood pressure (mm Hg)	75 ± 10	75 ± 10	0.2
Risk factors and cardiovascular antecedents			
Previous MI	540 (43)	144 (47)	0.3
Diabetes	152 (12)	38 (12)	1.0
Hypertension	435 (35)	159 (51)	<0.01
Previous stroke	28 (2)	14 (5)	0.03
Peripheral vascular disease	62 (5)	33 (11)	<0.01
Current smoker	363 (29)	53 (17)	<0.01
Cholesterol-lowering diet	217 (17)	76 (25)	0.01
Family history of CAD	372 (30)	76 (25)	0.07
Ejection fraction (%)	62 ± 11	61 ± 13	0.2
Single-vessel disease	818 (66)	175 (56)	0.01
Multivessel disease	430 (35)	135 (44)	0.01
Clinical presentation			
Stable angina*	618 (50)	164 (53)	0.4
Unstable angina	618 (50)	164 (53)	0.4
Treated vessel†			
RCA	484 (30)	128 (30)	0.9
LAD	766 (47)	207 (48)	0.9
LCx	371 (23)	98 (27)	0.9
Lesions treated per patient	1.3 ± 0.6	1.4 ± 0.7	0.03
Lesion type			
A	325 (20)	70 (16)	0.07
B1	566 (35)	153 (36)	0.9
B2	540 (33)	150 (35)	0.6
C	185 (11)	58 (14)	0.3
Lesions treated with stent	910 (56)	245 (57)	0.9
Lipids (mg/dl)			
Total cholesterol	200 ± 31	200 ± 33	0.9
LDL cholesterol	133 ± 29	131 ± 31	0.4
HDL cholesterol	37 ± 12	39 ± 12	<0.01
Triglycerides	154 ± 68	150 ± 69	0.5
Serum creatinine (mg/dl)	1.11 ± 1.7	1.33 ± 2.8	<0.01
Creatinine clearance (ml/min)	80 ± 18	47 ± 7	<0.01
Baseline medication			
ASA	1,221 (98)	299 (97)	0.2
Ticlopidine	862 (69)	238 (77)	<0.01
ACE inhibitor	319 (26)	107 (35)	<0.01
β Blocker	902 (72)	220 (71)	0.7

Values are mean ± SD or numbers (percentages).
*Includes patients who had silent ischemia
†Categories are not mutually exclusive
ACE = angiotensin-converting enzyme; ASA = aspirin; CAD = coronary atherosclerotic disease; HDL = high-density lipoprotein; LAD = left anterior descending artery; LCx = left circumflex artery; LDL = low-density lipoprotein; MI = myocardial infarction; RCA = right coronary artery.

and at 52, 104, and 156 weeks. All biochemical analyses were performed at a central laboratory (Analytico Medinet, Breda, The Netherlands). Creatinine clearance was calculated according to the formula proposed by Cockcroft and Gault[2]: creatinine clearance (milliliter/minute) = (140 − age) × weight (kilograms) ÷ 72 × serum creatinine (milligrams/deciliter) (× 0.85 for women).[2]

Clinical end points: Outcomes were evaluated as a composite of atherosclerotically related adverse cardiac events, defined as the incidence of cardiac death (all deaths except those unequivocally related to a noncardiac cause), nonfatal myocardial infarction (new pathologic Q waves or a total plasma creatine kinase level >2 times the normal upper limit with the MB isoenzyme), and all reinterventions (surgical or percutaneous) not caused by coronary restenosis occurring after the index procedure. Atherosclerotically related adverse cardiac events were a predefined end point of LIPS,[1] based on the demonstrated benefit of fluvastatin after percutaneous intervention being unrelated to any effect of the drug on restenosis.[3] In addition, the incidence of target lesion revascularization was analyzed in the 2 renal function groups.

Statistical analysis: All analyses were carried out on an intent-to-treat basis. Continuous variables were expressed as mean ± SD and were compared with Student's unpaired *t* test. Fisher's exact test was used for categorical variables, and Wilcoxon's scores were used for categorical variables with an ordinal scale. Discrete variables were expressed as counts and percentages and were compared in terms of relative risks and 95% confidence intervals (CIs). All statistical tests were 2-tailed. Event-free survival distribution was estimated according to the Kaplan-Meier method, and overall incidence of adverse events was tested with the log-rank test. Cox's proportional hazards models were used to assess decreased risk of adverse events.

For illustrative purposes, patients were assigned to 1 of 2 groups according to baseline value of creatinine clearance; abnormal creatinine clearance was defined as a value in the lowest quintile (<55.9 ml/min). This restrictive definition was applied in accordance with the LIPS study protocol, which excluded patients who had markedly impaired renal function. All testing to assess the effect of renal function on outcomes was performed using baseline creatinine clearance as a continuous numeric variable. Estimated risk ratios were calculated from the observed data, with mean clearance of the entire study population as a reference point for the placebo group (risk ratio 1). Creatinine clearance measurements were converted by logarithmic transformation to normalize distribution of the data.

All baseline clinical, angiographic, and procedural characteristics available in the study database were tested to evaluate their relation to the incidence of clinical adverse events. Variables presenting a univariate p value <0.1 were tested as candidates in a

TABLE 2 Incidence of Adverse Coronary Atherosclerotic Events at Follow-up According to Renal Function at Baseline and Treatment Allocation

	Normal Renal Function			Renal Impairment		
	Placebo (n = 617)	Fluvastatin (n = 631)	p Value*	Placebo (n = 160)	Fluvastatin (n = 150)	p Value*
Adverse coronary atherosclerotic events†	125 (20)	99 (16)	0.04	47 (29)	23 (15)	0.004
Cardiac death	14 (2)	7 (1)	0.1	3 (2)	3 (20)	1.0
Noncardiac death	0	0	—	0	0	—
All-cause death	14 (2)	7 (1)	0.1	3 (2)	3 (2)	1.0
Cardiac death/myocardial infarction	37 (6)	28 (4)	0.3	13 (8)	7 (5)	0.3
All-cause death/myocardial infarction	37 (6)	28 (4)	0.3	13 (8)	7 (5)	0.3

Values are numbers of patients (percentages).
*Placebo versus fluvastatin by Fisher's exact test.
†Cardiac death, nonfatal myocardial infarction, and reinterventions not related to restenosis.

TABLE 3 Risk of Adverse Coronary Atherosclerotic Events* at Follow-up According to Creatinine Clearance (Logarithmic Transformation) at Baseline and Treatment Allocation (derived from Cox's proportional hazards analysis)

	Hazard Ratio (95% CI)	p Value
Effect of fluvastatin treatment on the overall population	0.69 (0.55–0.87)	0.002
Effect of baseline creatinine clearance on the overall population (pooled over treatment allocation)	0.99 (0.98–0.99)	0.02
Effect of baseline creatinine clearance on patients who received placebo	0.99 (0.98–0.99)	0.01
Effect of baseline creatinine clearance on patients who received fluvastatin	1.0 (0.99–1.0)	0.63

*Cardiac death, nonfatal myocardial infarction, and reinterventions not related to restenosis.

multivariate analysis, and a final model was constructed by stepwise selection of the most significant variables (the following variables were selected from univariate analyses: allocated treatment, creatinine clearance, stable/unstable angina, smoking status, high-density lipoprotein cholesterol levels, gender, hypertension, diabetes, previous stroke, previous myocardial infarction, cholesterol-lowering diet, height, body mass index, diastolic blood pressure, systolic blood pressure, multivessel disease, pathologic Q wave in lead aVL, number of stents implanted, and number of sites with Thrombolysis In Myocardial Infarction grade 3 flow).

Lipid profiles and clearance-time profile were analyzed by analysis of covariance models that incorporated baseline values as covariates and added factors of treatment, number of visits, and renal function subgroup with all possible interaction terms. To evaluate the relation between occurrence of clinical events and behavior of renal function over time, separate analyses were performed to evaluate the clearance-time profile for patients who had adverse events during follow-up and those who did not.

RESULTS

Patient population: Between April 1996 and October 1998, 1,677 patients were enrolled in the LIPS. Complete data for creatinine clearance calculation were available for 1,558 patients (92.9%) and were included in the present study. Table 1 lists baseline characteristics of 1,248 patients who had normal renal function (creatinine clearance above the first quintile or ≥55.9 ml/min) and of 310 patients who had impaired renal function (creatinine clearance in the lowest quintile or <55.9 ml/min). Overall, patients who had renal impairment were more likely to be older, to be women, to be lighter and shorter, and to have more severe coronary artery disease and co-morbidities.

Four groups were considered for analysis: (1) patients who had normal renal function and received placebo (n = 617), (2) patients who had normal renal function and received fluvastatin (n = 631), (3) patients who had impaired renal function and received placebo (n = 160), and (4) patients who had impaired renal function and received fluvastatin (n = 150). Baseline characteristics did not differ between fluvastatin and placebo groups (pooled across renal function categories) except that patients who received fluvastatin were taller (170 ± 8 vs 169 ± 8 cm, p = 0.02) and heavier (77 ± 11 vs 76 ± 11 kg, p <0.01) and showed a higher prevalence of diabetes (14% vs 10%, p <0.01).

Cardiovascular events: Patients were followed for a mean of 3.8 ± 0.1 years. Table 2 lists incidences of coronary atherosclerotic events according to allocated treatment and presence of renal impairment. Overall, fluvastatin therapy significantly decreased the incidence of adverse events (hazard ratio 0.69, 95% CI 0.55 to 0.87, p = 0.002; Table 3). Moreover, baseline creatinine clearance (logarithmic transformation) was inversely associated with an incidence of adverse events in the overall population pooled by treatment (hazard ratio 0.99, 95% CI 0.98 to 0.99, p = 0.02; Table 3). However, when analyzed separately, baseline creatinine clearance

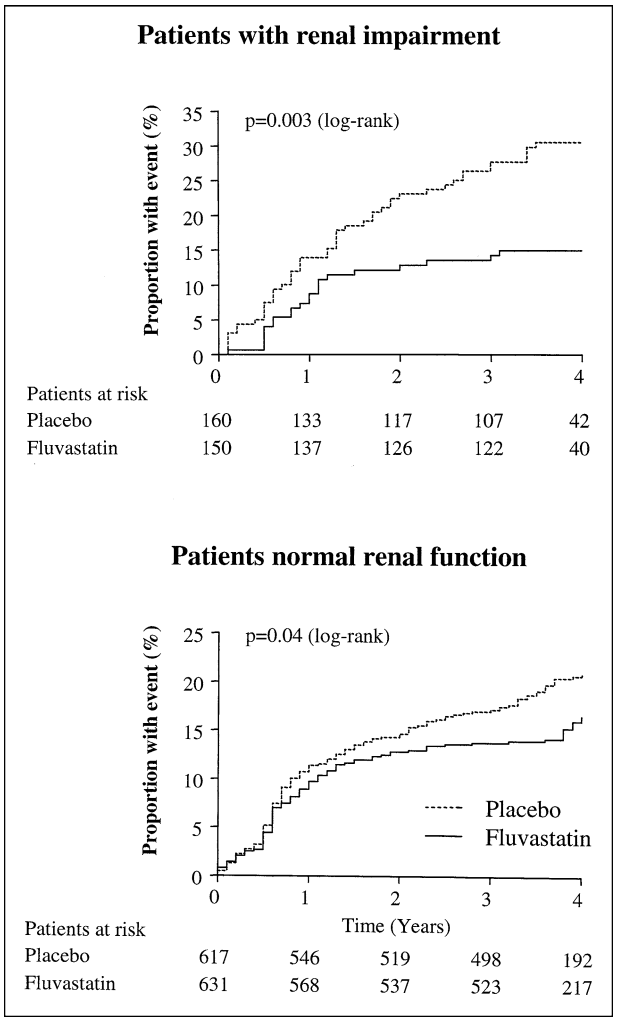

FIGURE 1. Cumulative risk of atherosclerotically related adverse cardiac events (cardiac death, nonfatal myocardial infarction, and all reinterventions not caused by coronary restenosis) in patients who had renal impairment *(top)* versus those who had normal renal function *(bottom)* who received placebo or fluvastatin.

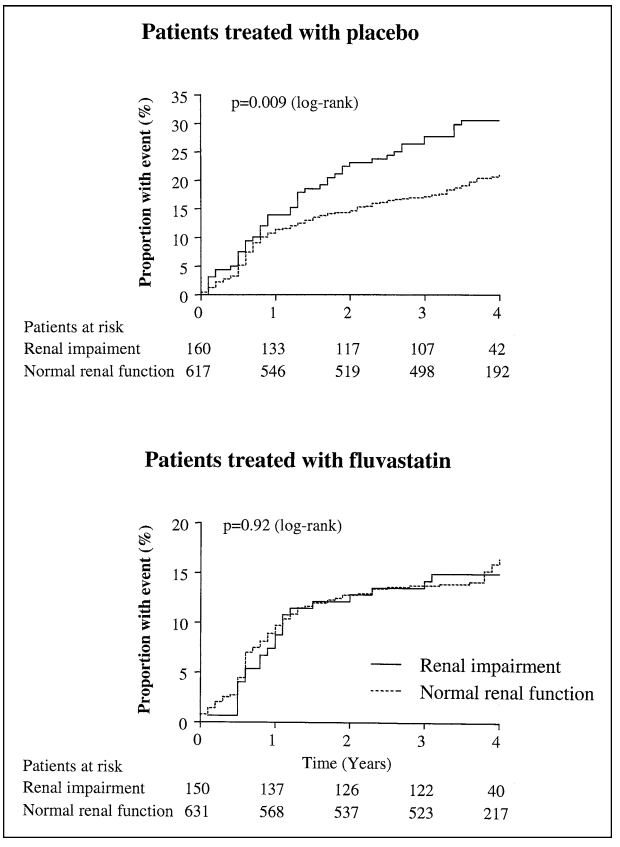

FIGURE 2. Cumulative risk of atherosclerotically related adverse cardiac events (cardiac death, nonfatal myocardial infarction, and all reinterventions not caused by coronary restenosis) in patients who received placebo *(top)* versus those who received fluvastatin *(bottom)* according to baseline renal function.

was significantly associated with outcomes of patients who received placebo (hazard ratio 0.99, 95% CI 0.982 to 0.998, p = 0.01), whereas no association was noted among patients who received fluvastatin (hazard ratio 1.0, 95% CI 0.99 to 1.0, p = 0.63; Table 3). Figures 1 and 2 show Kaplan-Meier curves of patients who received fluvastatin or placebo grouped according to presence of renal impairment or normal renal function. Among patients who received placebo, curves of patients who had renal impairment versus those who did not began to diverge after approximately 1 year (p = 0.009 by log-rank test; Figure 2). Conversely, among patients who received fluvastatin, curves of adverse events of patients who had renal impairment versus those of patients who had normal renal function remained overlapped throughout follow-up (p = 0.92 by log-rank test; Figure 2). No differences were observed in the incidence of repeat revascularization due to restenosis between patients who had renal impairment and those who did not (4.4% vs 5.2%, respectively, p = 0.7).

Lipoprotein levels and renal function outcome: Baseline lipoprotein levels were similar in the 2 renal function groups, with the exception of high-density lipoprotein cholesterol levels (Table 1). By 6 weeks, fluvastatin significantly decreased levels of low-density lipoprotein cholesterol compared with placebo in patients who had renal impairment (median change with fluvastatin −24%, 95% CI −28 to −20 vs +13%, 95% CI +9 to +17, p <0.001) and those who had normal renal function (−28%, 95% CI −30 to −25% vs +11%, 95% CI +9 to +13%, p <0.001). The decrease was similar in patients who had renal impairment and those who did not and was maintained throughout the study. At the end of the study, no significant differences in triglyceride levels were observed between treatment groups. Levels of high-density lipoprotein cholesterol increased by a median of 12%, regardless of treatment allocation or baseline renal function.

Renal function remained stable throughout follow-up and the predicted clearance-time profile was not influenced by fluvastatin therapy, regardless of baseline creatinine clearance (Figure 3). No significant changes were observed in renal function between

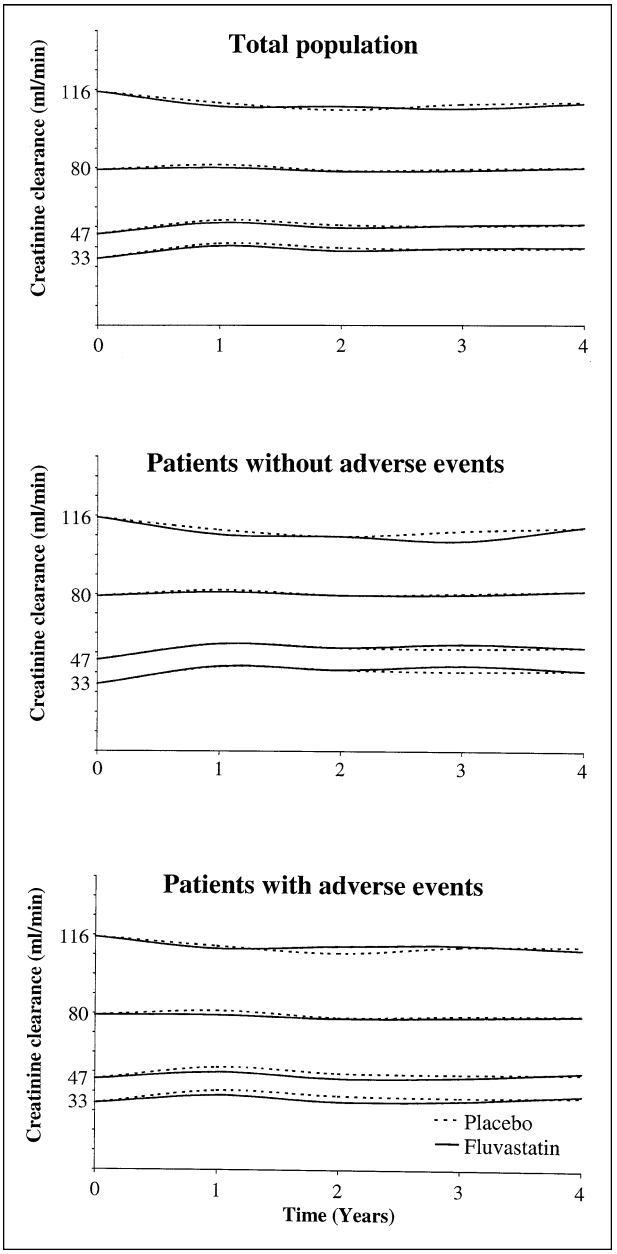

FIGURE 3. Predicted changes in creatinine clearance (milliliters/minute) throughout follow-up in patients who had been randomized to receive placebo or fluvastatin. Four baseline clearance levels are shown: 47 ml/min (actual mean clearance of patients who had renal impairment), 80 ml/min (actual mean clearance of patients who had normal renal function), 33 ml/min (mean clearance of patients who had renal impairment −2 SD), and 116 ml/min (mean clearance of patients who had normal renal function +2 SD). Changes in renal function are shown for the entire population *(top)*, patients who did not develop adverse events *(middle)*, and patients who developed ≥1 adverse event during follow-up *(bottom)*.

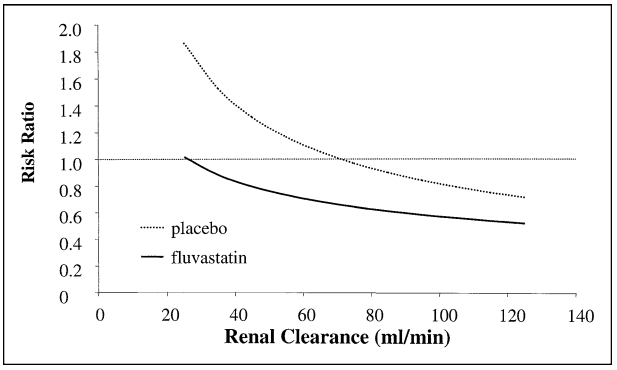

FIGURE 4. Estimated risk ratios as a function of creatinine clearance (millimeters/minute) in patients who had been randomized to receive fluvastatin or placebo. Hazard ratio curves were estimated according to Cox's proportional hazards model (risk ratios were calculated with the mean creatinine clearance of the entire study population chosen as a reference point for the placebo group, risk ratio 1).

TABLE 4 Multivariate Predictors of Adverse Coronary Atherosclerotic Events at Follow-up

	Hazard Ratio (95% CI)	p Value
Fluvastatin therapy	0.66 (0.52–0.83)	0.0005
Diabetes mellitus	1.57 (1.14–2.16)	0.006
Multivessel disease	1.33 (1.04–1.69)	0.02
No. of stents implanted	1.25 (1.04–1.51)	0.02
Creatinine clearance*	0.63 (0.42–0.95)	0.03

*Logarithmic transformation.

patients who had adverse events during follow-up and those who did not (Figure 3).

Predictors of increased cardiovascular risk: Figure 4 shows estimated risk ratios according to baseline creatinine clearance calculated by Cox's proportional hazards model from the observed data (mean clearance of the entire study population was chosen as a reference point for the placebo group, risk ratio 1). A progressive increase in the risk of long-term complications is predicted with lower values of creatinine clearance. However, fluvastatin therapy caused a downward shift and flattening of the entire risk ratio curve. Interestingly, a risk ratio of 1 was associated with a baseline creatinine clearance of ~70 ml/min in the placebo group but with a rate of only 25 ml/min in the fluvastatin group.

Multivariate Cox's proportional hazards analysis identified creatinine clearance as an independent predictor of atherosclerotically related adverse cardiac events (Table 4). Other variables significantly associated with an incidence of adverse events included fluvastatin therapy, diabetes mellitus, multivessel disease, and number of stents implanted during a procedure (Table 4).

DISCUSSION

The major finding of the present study is that low values of creatinine clearance at baseline significantly increases the incidence of coronary adverse atherosclerotic events after a first successful percutaneous coronary intervention and that this effect is virtually abolished by long-term therapy with fluvastatin. The benefit of fluvastatin in patients who have renal impairment could not be explained by a differential action on lipid levels or on renal function during follow-up. Moreover, no association was observed

between the incidence of adverse events and changes in renal function during follow-up.

In addition to procedures to alleviate symptoms and myocardial ischemia, secondary prevention of further adverse events constitutes a key paradigm in the long-term management of patients who have diagnosed coronary disease. Although the need for repeat intervention has been recognized as the major limitation of angioplasty, the newly introduced drug-eluting stents have been shown to markedly decrease restenosis rates.[4] In this context, adoption of procedures aimed at modifying the natural course of atherosclerotic disease (i.e., non–restenosis-related complications) becomes the main focus of attention after percutaneous control. In the present study, fluvastatin was shown to significantly decrease the incidence of adverse events after angioplasty in patients who had renal dysfunction and those who did not.

Secondary prevention strategies constitute a range of methods to decrease the effect of known risk factors on outcomes of patients who have diagnosed coronary disease. Ideally, management of a particular risk factor should decrease the risk of patients who receive treatment to the level of subjects who do not have the condition. Mild renal impairment has been identified as an important predictor of adverse events in patients who have previous cardiovascular disease.[5–12] Although diuretic-based blood pressure control and long-term ramipril therapy have been reported to improve clinical outcomes, the hazardous effect of mild renal impairment was only partly decreased by these therapies.[11,13] Pravastatin has recently been shown to decrease the incidence of events in patients who have renal dysfunction; in contrast to most reports, the presence of renal impairment did not influence late clinical outcomes in that study.[14] Moreover, the extent to which statins decreased the risk of future complications was not evaluated in relation to patients who had normal renal function.[14] In the present study, renal impairment significantly and independently impaired long-term clinical outcomes after coronary intervention. Notably, fluvastatin therapy equalized outcomes of patients who had renal impairment and those who had normal renal function, thus virtually abolishing the hazardous effect of renal dysfunction.

In contrast to previous studies,[15] no effect of fluvastatin therapy on renal function was observed during the 4-year follow-up. These results suggest that the benefit of fluvastatin was not mediated by a direct effect to stabilize or improve creatinine clearance. Moreover, occurrence of adverse events was not related to changes in renal function. In addition, the effect of fluvastatin in patients who had renal dysfunction could not be explained by a more pronounced lipid decrease in this group. These results suggest that the benefit of statins in patients who have renal impairment may be associated with mechanisms that are not related to a direct effect on kidney physiology and are independent of their lipid-lowering effects. Although not assessed in the present study, statins have been widely reported to exert beneficial effects on a variety of pathophysiologic atherogenic mechanisms that are altered in patients who have renal impairment.[16–24]

Study limitations: The present findings may not be extrapolated to all patients who have coronary heart disease, because only patients who underwent successful elective percutaneous interventions were included. Therefore, medically and surgically treated patients and those who had unsuccessful procedures were not represented in this study population. Further, the effect of fluvastatin in patients who had severe renal impairment was not assessed in the present study, and more detailed investigations of the nature of renal impairment (e.g., diagnosis of underlying renal pathology or assessment of microalbuminuria or proteinuria) and measurements of biochemical proatherogenic markers were not available. These limitations do not alter the overall conclusion that fluvastatin therapy had a clinically relevant effect in patients who had mild renal impairment.

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