The extent of late in-stent neointima formation is modified by treatment with pravastatin: a preliminary study with intravascular ultrasound

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Key words:
Intravascular ultrasound; Restenosis; Statins.

Background. **The aim of the present comparative, non-randomized intravascular ultrasound (IVUS) study was to test the effect of pravastatin on late neointima formation in stented *de novo* lesions.**

Methods. **The treatment group consisted of 28 consecutive patients in whom 31 stents were deployed; all patients were prescribed 40 mg daily of pravastatin for a mean follow-up period of 14 ± 3 months (group 1). The control group consisted of 27 consecutive patients in whom 30 stents were deployed; lipid-lowering treatment was not prescribed; the mean follow-up period for this group of patients was 13 ± 3 months (group 2). At follow-up IVUS images were acquired at a continuous 0.5 mm/s speed. IVUS measurements of the lumen area, stent area and neointima area were calculated within the stent at 0.5 mm intervals.**

Results. **The stent dimensions and technique of implantation were similar in the two groups. At follow-up the minimal lumen diameter at quantitative coronary angiography was slightly larger in group 1 than in group 2 (2.43 ± 0.58 vs 2.17 ± 0.59 mm, p = NS), while the late loss tended to be lower in group 1 than in group 2 (0.28 ± 0.39 vs 0.63 ± 0.37 mm, p = NS). At IVUS evaluation, the lumen and stent areas were similar in the two groups whereas the percent neointima area was significantly lower in group 1 than in group 2 (21 ± 11 vs 29 ± 11% respectively, p < 0.03).**

Conclusions. **Pravastatin treatment was associated with a significantly reduced late in-stent neointima formation as assessed at IVUS.**

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Introduction

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase are potentially capable of limiting smooth muscle cell proliferation[1-4]. Some studies addressed the impact of statin therapy on late restenosis after coronary balloon angioplasty[5-9] but provided conflicting results.

The mechanism of restenosis after balloon angioplasty, mainly due to late vessel shrinkage, could explain the lack of efficacy of statins. Because the mechanism of restenosis after stenting, unlike balloon angioplasty, is solely due to the proliferation of smooth muscle cells and to extracellular matrix formation within the stent struts[10], stenting represents a unique model for the investigation of the efficacy of drugs able to modify neointima formation. Thus, the aim of the present intravascular ultrasound (IVUS) study was to assess the efficacy of pravastatin in reducing late neointima formation after coronary stenting.

Methods

Patient population. In this comparative non-randomized multicenter (4 centers) study only non-diabetic patients with coronary artery disease, with the exception of myocardial infarction, who underwent interventional procedures from January 1998 to June 1998, were enrolled. With regard to the treatment group, 40 consecutive patients with mild hypercholesterolemia, enrolled in an observational, non-randomized, serial IVUS study on the assessment of atherosclerosis in response to pravastatin treatment, were considered. Of the 40 patients, 30 underwent stent implantation for the treatment of short (< 15 mm), *de novo* lesions in vessels with a reference diameter

> 2.5 mm and were included in the present study. IVUS assessment was obtained at the end of follow-up (14 ± 3 months) in 28 patients (31 stents) (group 1). The control group (group 2) consisted of 27 consecutive patients (30 stents) with total cholesterol serum levels < 230 mg/dl, who underwent stenting for the treatment of lesions with the same characteristics as those described in group 1 and who were not treated with lipid-lowering drugs at the time of intervention and during follow-up. In the control group follow-up IVUS assessment was performed at 13 ± 3 months.

Stenting procedures and medication protocols. In all cases elective or bail-out stenting of *de novo* native coronary artery lesions was performed using stents with a cellular design and deployed at an inflation pressure > 10 atm. Multiple stents were positioned only in case of residual dissection. Heparin (7000 IU) was administered after insertion of the arterial sheath. An additional bolus of heparin was administered, when necessary, to maintain an activated clotting time > 250 s. Intracoronary nitroglycerin (200 μg) was given before acquisition of the basal angiogram and repeated before the final and follow-up angiograms.

Ticlopidine (500 mg daily) was given for 4 weeks and chronic treatment with aspirin (100 mg daily) was instituted. In group 1 pravastatin therapy, at the dosage of 40 mg daily, was started on the day of intervention and continued until follow-up assessment.

Lipid measurements. The following measurements were performed at baseline and at 12 months: total cholesterol, LDL and HDL cholesterol, lipoprotein(a), and apolipoproteins A1, A2, B and E.

Quantitative coronary angiography. Quantitative coronary angiography (QCA) analysis was performed offline with a computer assisted system using an automated edge detection algorithm (MEDIS, Cardiovascular Angiography Analysis System II, Pie Medical Data, Maastricht, The Netherlands). QCA analyses were performed at the European Imaging Laboratory, Rome, Italy, by observers who were unaware of the treatment allocation. The treated segment was analyzed using two orthogonal views[11]. Analyses were performed pre-intervention, post-intervention and at follow-up. The primary angiographic endpoint of the study was the measurement of the late lumen loss, defined as the post-intervention stent minimal lumen diameter minus the minimal lumen diameter at follow-up. The acute gain was defined as the post-intervention stent minimal lumen diameter minus the minimal lumen diameter before intervention. Angiographic restenosis was defined as a diameter stenosis ≥ 50% at the treated site.

Intravascular ultrasound assessment. *Image acquisition.* Follow-up IVUS images of stented segments were obtained with a 3.2F short monorail imaging catheter (Cardiovascular Imaging Systems, Inc., Boston Scientific Co., Maple Grove, MN, USA) after written informed consent had been obtained. The IVUS catheter incorporates a 30 MHz single-element beveled transducer mounted at the distal end of the catheter and rotated at 1800 rpm. After coronary angiography, patients were administered heparin (5000 IU i.v.) via the arterial sheath and nitroglycerin (200 μg i.c.). The imaging probe was positioned distal to the stented segment and was mechanically pulled backwards at a speed of 0.5 mm/s. IVUS images were recorded on high-resolution s-VHS videotape for off-line analysis.

Quantitative intravascular ultrasound analysis. The cross-sectional vessel area, stent area, and lumen area measurements were performed every second of videotape. Therefore, each stent was axially divided into several 0.5 mm segments. In each stented segment the following measurements were obtained: mean lumen area, mean stent area and mean area of neointima formation, defined as echogenic material within the stent and calculated as stent area minus lumen area. The percent neointima area was also calculated as (stent area - lumen area/stent area) × 100. IVUS analyses were also obtained in the cross-section with most severe narrowing (minimal lumen area). Measurements were performed using an algorithm for semiquantitative analysis (TapeMeasure, INDEC Systems, Inc., Mountain View, CA, USA)[10,12]. The reproducibility of the IVUS measurements was calculated in a blind comparison performed by two independent operators on 20 stents (10 stents of group 1 and 10 stents of group 2). The correlation coefficients of repeated measurements of the mean stent and lumen areas and the mean percent neointima area were 0.99, 0.99, and 0.98 respectively.

Statistical analysis. Continuous variables are expressed as mean ± SD. The two-tailed Student's t test was used for continuous variables. A χ^2 test was used to detect differences between categorical variables. Linear regression analyses were performed to correlate the percent neointima area and lipid variables. Results are expressed as mean ± SD. A p value of < 0.05 was considered statistically significant.

Results

Patient and procedural characteristics. The clinical characteristics of the study patients and the procedural variables are shown in tables I to III[13]. No significant differences regarding either the clinical and angiographic data or the implantation technique were found between the two groups.

Clinical outcome. Stents were successfully deployed in all group 1 and group 2 cases. At 12 month follow-up all patients of group 1 were alive and none had ex-

Table I. Patient population.

	Group 1 (n=28)	Group 2 (n=27)	p
No. stents	31	30	NS
Stent/patient	1.1	1.1	NS
Age (years)	60.1 ± 6.8	63.4 ± 9.8	NS
Men	23 (82%)	21 (78%)	NS
Risk factors			
Baseline total cholesterol (mg/dl)	228 ± 41	214 ± 36	NS
Smokers	11 (39%)	13 (48%)	NS
Hypertension	12 (43%)	11 (41%)	NS
Familiarity	5 (18%)	4 (15%)	NS
Clinical syndrome			
Stable angina	11 (40%)	12 (44%)	NS
Unstable angina	15 (53%)	12 (44%)	NS
Silent ischemia	1 (7%)	3 (12%)	NS

Table II. Angiographic characteristics.

	Group 1 (n=28)	Group 2 (n=27)	p
No. diseased coronary arteries			
1	15 (54%)	14 (52%)	NS
2	8 (28%)	8 (29%)	NS
3	5 (18%)	5 (19%)	NS
Treated vessel			
LAD	16 (57%)	17 (63%)	NS
LCx	7 (25%)	4 (15%)	NS
RCA	5 (18%)	6 (22%)	NS
ACC/AHA[13] type of lesion			
A	5 (18%)	5 (18%)	NS
B1	13 (46%)	12 (45%)	NS
B2	8 (29%)	9 (33%)	NS
C	2 (7%)	1 (4%)	NS

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

Table III. Procedural characteristics.

	Group 1 (n=28)	Group 2 (n=27)	p
Max inflation pressure (atm)	12.3 ± 4.0	12.2 ± 1.4	NS
Stent length (mm)	14.9 ± 3.4	15.2 ± 3.4	NS
Stent/patient	1.1	1.01	NS
Stent diameter (mm)	3.3 ± 0.3	3.4 ± 0.4	NS
Stent type			
GFX*	17 (55%)	16 (53%)	NS
Multilink Duet**	6 (19%)	6 (20%)	NS
NIR***	8 (26%)	8 (27%)	NS

* = Arterial Vascular Engineering, Santa Rosa, CA, USA; ** = Guidant, Santa Clara, CA, USA; *** = Scimed, Boston Scientific Corporation, Maple Grove, MN, USA.

perienced a myocardial infarction. Two group 1 patients underwent a new procedure for recurrent angina attributable to the progression of untreated atherosclerotic lesions. In group 2 all patients were alive; in 1 patient a non-Q wave myocardial infarction, attributable to severe in-stent restenosis, occurred. Three group 2 patients had recurrent angina due to in-stent restenosis and were submitted to a new procedure.

Angiographic results. The results of QCA analyses are summarized in table IV. There were no baseline differences in the minimal lumen diameter or reference di-

Table IV. Quantitative coronary angiography.

	Group 1 (n=28)	Group 2 (n=27)	p
Pre-intervention			
Reference diameter (mm)	3.08 ± 0.75	3.20 ± 0.45	NS
Minimal lumen diameter (mm)	0.75 ± 0.67	0.81 ± 0.73	NS
Diameter stenosis (%)	74 ± 24	70 ± 26	NS
Post-stenting			
Reference diameter (mm)	3.24 ± 0.46	3.34 ± 0.24	NS
Minimal lumen diameter (mm)	2.71 ± 0.54	2.80 ± 0.28	NS
Diameter stenosis (%)	17 ± 8	18 ± 9	NS
Follow-up			
Reference diameter (mm)	3.10 ± 0.47	3.23 ± 0.34	NS
Minimal lumen diameter (mm)	2.43 ± 0.58	2.17 ± 0.59	NS
Diameter stenosis (%)	22 ± 11	33 ± 17	NS
Late loss (mm)	0.28 ± 0.39	0.63 ± 0.37	NS
Acute gain (mm)	1.96 ± 0.43	1.99 ± 0.51	NS

ameter. The mean angiographic follow-up data were obtained at 14 ± 3 months in group 1 and at 13 ± 3 months in group 2 (p = NS). At follow-up the minimal lumen diameter was slightly larger in group 1 than in group 2 (2.43 ± 0.58 vs 2.17 ± 0.59 mm, p = NS), while the late loss tended to be less in group 1 than in group 2 (0.28 ± 0.39 vs 0.63 ± 0.37 mm, p = NS). Restenosis was angiographically diagnosed in 1 of the 31 stents deployed in group 1 patients (3%) and in 3 of the 30 stents deployed in group 2 patients (10%).

Intravascular ultrasound analysis. The results of IVUS evaluation are shown in tables V and VI. The mean stent areas were similar in the two groups whereas the neointima and percent neointima areas were significantly greater in group 2 than in group 1. Analyses were repeated for the stents deployed in the left anterior descending artery and confirmed a significantly greater degree of late neointima formation in group 2 than in group 1.

Modification of lipid variables and correlation with neointima formation. The mean total cholesterol and LDL cholesterol serum levels were slightly higher in group 1 than in group 2 (230 ± 43 vs 212 ± 36 mg/dl and 144 ± 32 vs 137 ± 33 mg/dl respectively, p = NS).

Table V. Intravascular ultrasound measurements obtained at follow-up.

	Group 1 (n=28)	Group 2 (n=27)	p
Lumen area (mm^2)	6.03 ± 2.03	5.31 ± 1.37	NS
Stent area (mm^2)	7.61 ± 2.10	7.51 ± 1.56	NS
Neointima area (mm^2)	1.58 ± 0.76	2.20 ± 1.02	< 0.04
Neointima area (%)	21 ± 11	29 ± 11	< 0.03
Narrowest site lumen area			
Lumen area (mm^2)	4.75 ± 1.80	3.84 ± 1.22	NS
Stent area (mm^2)	6.59 ± 1.87	6.58 ± 1.49	NS
Neointima area (mm^2)	1.84 ± 1.28	2.74 ± 0.26	< 0.05
Neointima area (%)	27 ± 16	41 ± 23	< 0.02

Table VI. Intravascular ultrasound measurements in the left anterior descending artery lesions.

	Group 1 (n=28)	Group 2 (n=27)	p
Lumen area (mm^2)	5.83 ± 2.22	5.10 ± 1.37	NS
Stent area (mm^2)	7.18 ± 2.40	7.31 ± 1.56	NS
Neointima area (mm^2)	1.35 ± 0.56	2.21 ± 1.02	< 0.03
Neointima area (%)	19.4 ± 10.3	30.2 ± 11.3	< 0.04
Narrowest site lumen area			
Lumen area (mm^2)	4.90 ± 1.72	3.65 ± 1.22	NS
Stent area (mm^2)	6.25 ± 1.96	6.36 ± 1.43	NS
Neointima area (mm^2)	1.35 ± 0.97	2.71 ± 1.04	< 0.01
Neointima area (%)	21.0 ± 12.7	42.8 ± 14.5	< 0.01

The mean level of HDL cholesterol was 44 ± 8 mg/dl in group 1 and 39 ± 7 mg/dl in group 2 (p = NS). No significant changes in lipid variables were observed in the control group during the study. Compared to baseline values, a significant decrease in the mean total cholesterol, mean LDL cholesterol and apolipoproteins B and E and a significant increase in HDL cholesterol and apolipoproteins A1 and A2 were found in group 1 at follow-up (Table VII).

The correlation coefficients between the LDL cholesterol decrease and the neointima area and that between the LDL cholesterol decrease and the percent neointima area were not statistically significant (r = -0.27 and r = -0.25 respectively).

Discussion

Rationale for statin use for the inhibition of neointima formation. The rationale for using statin therapy for the prevention of restenosis emerges from the following observations: 1) statin therapy potentially inhibits smooth muscle cell proliferation[1-4]; 2) statins can reduce the levels of serum C-reactive protein, a systemic marker of inflammation which has been shown to identify a subset of patients prone to restenosis after percutaneous procedures[14-16].

Previous experimental findings provided evidence that high dose therapy with 3-hydroxy-3-methylglutaryl coenzyme A inhibitors prevents vascular smooth muscle cell formation after vascular injury[1-4]. Indeed, Indolfi et al.[2] assessed the impact of 40 mg/kg/day of simvastatin on *in vivo* vessel smooth muscle cell proliferation by means of balloon injury and stent application in the common carotid arteries of rats. Simvastatin significantly reduced the in-stent neointima formation by 66%. Furthermore, analysis of the CARE study revealed that randomization to pravastatin at 40 mg daily resulted in a 7% decrease in the serum levels of C-reactive protein[14]. Since it was shown that cardiac events, used as surrogates for restenosis, were more frequent in patients with elevated C-reactive protein levels at 48 and 72 hours after stenting[15,16], a reduction in the serum levels of C-reactive protein by means of statins may elicit a long-term favorable effect.

Clinical studies on statin therapy after balloon angioplasty and stenting. Despite evidence of the *in vitro* reduction in smooth muscle cell proliferation and of a favorable effect in terms of reduced serum levels of C-reactive protein, statin therapy was not consistently found to reduce restenosis after balloon angioplasty. While previous randomized studies showed that the 6 month restenosis rate is not modified by statin administration[5-7], more recently Mulder et al.[8], in a multicenter study adopting a late angiographic 24 month follow-up, demonstrated that statin use is associated with a significant reduction in the incidence of late restenosis. To justify these conflicting results it is reasonable to speculate that statins can reduce late restenosis by means of a long-term favorable effect on vessel remodeling, that cannot be observed when coronary angiography is scheduled at 6 months of follow-up[8,9].

Besides explanations that can be given to justify the conflicting results obtained with statin therapy in the setting of balloon angioplasty, it has to be stressed that these studies were not tailored to define the effect of statins on late neointima formation as the predominant cause of restenosis. In fact, the important contribution of late shrinkage to the process of late restenosis after balloon angioplasty may have masked the antiproliferative effects of statins. Previous studies based on serial IVUS assessment clarified that the mechanisms of late restenosis after balloon angioplasty and after stent implantation are different[10,17]. Whereas after balloon angioplasty, late shrinkage plays a major role in restenosis, leading to a 60-70% lumen reduction, the only mechanism responsible for late restenosis after stenting is the proliferation of the neointima; in fact, the scaffolding properties of the stent prevent late vessel recoil. Therefore, unlike balloon angioplasty, stenting represents a unique model for studying the effects of drugs influencing the process of neointima formation.

The present IVUS study confirms the findings by Walter et al.[18] who provided a first preliminary evidence that statin therapy can reduce stent restenosis. The authors performed a retrospective angiographic analysis on 525 consecutive patients treated with stenting and found a lower restenosis rate in the group in which treatment with statins was instituted (25 vs 38% respectively). As a major drawback, in the retrospective

Table VII. Baseline and follow-up lipid profile in pravastatin treated patients.

	Baseline	Follow-up	p
Total cholesterol (mg/dl)	230 ± 43	193 ± 23	< 0.005
LDL cholesterol (mg/dl)	171 ± 39	144 ± 32	NS
HDL cholesterol (mg/dl)	44 ± 8	53 ± 7	< 0.05
Triglycerides (mg/dl)	145 ± 32	114 ± 24	< 0.005
Apolipoprotein A1 (mg/dl)	131 ± 24	163 ± 39	< 0.05
Apolipoprotein B (mg/dl)	123 ± 32	97 ± 31	< 0.01
Apolipoprotein A2 (mg/dl)	21 ± 6	37 ± 4	< 0.001
Apolipoprotein E (mg/dl)	5 ± 2	3 ± 1	< 0.05

study by Walter et al. different statin regimens were adopted in the treated group and a relevant percentage of treated patients (19%) were already on statin therapy. Due to this latter limitation, the authors could not speculate whether pre-treatment with statins was necessary to improve the restenosis rate after stenting.

In our study we found that the extent of late neointima formation was reduced in the group treated with pravastatin at a dose of 40 mg daily. Namely, we found a significant 28% reduction in the mean neointima area (1.58 ± 0.76 vs 2.20 ± 1.02 mm^2, $p < 0.04$) and a 27% reduction in the mean percent neointima area (21 ± 11 vs $29 \pm 11\%$, $p < 0.03$). Since only patients without previous treatment with statins were enrolled in our study, we provided the first demonstration that the use of pravastatin, starting on the day of the procedure, can reduce stent restenosis. The possibility of reducing late neointima formation by instituting treatment on the day of procedure obviously represents a substantial advantage since pre-treatment would necessitate deferral of the intervention that, in certain clinical settings such as acute coronary syndromes, would not be possible.

The use of intravascular ultrasound to assess late in-stent neointima formation. The use of IVUS to interrogate stented segments at follow-up provided valuable information in addition to that obtained at QCA evaluation, enabling an accurate assessment of the area of neointima formation. In fact, QCA permits only measurements of the vessel lumen reduction induced by the neointima and therefore provides an indirect estimation of neointima formation. It was recently shown that IVUS assessment of neointima formation necessitates smaller sample sizes than QCA for the documentation of significant reductions of in-stent restenosis[19,20]. Consistently with this observation, in the present study, QCA assessment showed only a trend towards a reduction of lumen diameter in the group treated with pravastatin, while IVUS allowed for the identification of a significant decrease in late neointima formation.

Study limitations. As a major limitation, the present study has a comparative non-randomized design. In fact, the IVUS results obtained in the group treated with statins were matched with the IVUS assessment performed at follow-up in a consecutive series of cases and obtained in the same centers. However, in spite of the non-randomized design, the study focused on the comparison of two selected and homogeneous groups of lesions; in fact, the clinical and angiographic characteristics capable of influencing late restenosis, such as diabetes, acute myocardial infarction, restenotic lesions, lesions in small vessels and long lesions were excluded from the analysis. If the real effects of statin therapy on in-stent restenosis are to be further defined, our preliminary results need to be confirmed by large randomized studies.

Post-stenting IVUS assessment was not performed; therefore we could not exclude the occurrence of plaque prolapse and of late stent recoil, two conditions that may affect the long-term assessment of the in-stent neointima after stent implantation. Since plaque prolapse within stent struts is an uncommon finding and since the same type of stents were used in the two groups, it is unlikely that the lack of post-stenting IVUS assessment would modify the comparison of late neointima formation in the two groups.

Our study was performed in a selected group of lesions, including only short *de novo* lesions in target vessels with a reference diameter > 2.5 mm. Consequently, in both groups we obtained low restenosis rates. Indeed, in the group treated with pravastatin the rate of restenosis was only 4%. Therefore, these preliminary findings cannot be extended to the entire population of patients with coronary artery disease and undergoing stent implantation.

Pravastatin at the dosage of 40 mg daily was used in the present study to assess the impact of statin therapy on stent restenosis. However, data derived from an experimental study showed that other statins can inhibit vessel smooth muscle cell proliferation at lower concentrations than pravastatin[21]. Therefore, further studies are warranted to verify the efficacy of other statins on stent restenosis[6].

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