Effect of Lipid Levels and Lipid-Lowering Therapy on Restenosis after Coronary Artery Stenting

STAMATIOS LERAKIS, MD; MIKHAEL F. EL-CHAMI, MD; AMAR D. PATEL, MD; EMIR VELEDAR, PhD; ELIAS ALEXOPOULOS, MD; ACHILLEAS ZACHAROULIS, MD; AGGELIKI TRIANTAFYLLOU, MD, PhD

ABSTRACT: *Background:* Recent experimental and clinical data suggest that lowering serum lipid levels with statins may prevent or delay the process of restenosis. The purpose of this trial is to determine whether lipid levels relate to restenosis and/or whether statin therapy can prevent or delay the process of restenosis after intracoronary stenting. *Methods:* One hundred thirty-six patients who underwent single coronary artery stenting from June 1995 to June 1997 in our institution were included in the study. All these patients were followed for at least 9 months (mean 392 ± 148 days) for major adverse cardiac events (MACE). We defined as MACE the occurrence of death, myocardial infarction, or need for target lesion revascularization. From this cohort, 103 patients had at least one lipid parameter from the lipid profile evaluated within 2 months from the date of the procedure. Patients who had the stent because of an acute myocardial infarction were included in the study only if their lipid profile was evaluated before or at least 6 weeks after the event. Patients with triglyceride levels above 500 had both triglyceride and low-density lipoprotein cholesterol levels excluded from the statistical analysis. Patients were divided into two groups based on lipid levels: normal (Group I; n = 31) and elevated (Group II; n = 72). Patient outcomes were also analyzed by statin therapy use. *Results:* There was no significant difference in MACE rates between the two groups when outcomes were analyzed by lipid levels (22.6% versus 20.8% $P = 0.8$). Furthermore, outcomes were analyzed by use of statin therapy (Group III, n = 53, on statin versus Group IV, n = 50, on no statin). There was also no difference in MACE rates between the two groups (20.8% versus 22%; $P = 0.8$). *Conclusion:* The process of restenosis has unique features that differentiate it from atherosclerosis. Although lipid-lowering therapy is crucial in delaying the process of atherosclerosis, its role in the prevention of restenosis is yet to be proven. **KEY INDEXING TERMS:** Restenosis; Lipid lowering; Cholesterol. **[Am J Med Sci 2006;331(5):270–273.]**

Although the use of coronary stenting has increased dramatically, restenosis remains a significant concern. Several pathophysiologic characteristics suggest similarities between the processes of restenosis and atherosclerosis. Initially, large clinical trial data from the Scandinavian Simvastatin Survival study,[1] the Cholesterol and Recurrent Events trial,[2] the Long-term Intervention with Pravastatin in Ischemic Disease,[3] and the Heart Protection Study[4] demonstrated that lipid-lowering drug therapy was an efficacious long-term strategy to reduce cardiovascular risk. Other trials demonstrated that "statins" are also an intervention to be used in the near-term management of patients after acute coronary syndrome or percutaneous coronary intervention (PCI).[5–11] On the other hand, the efficacy data regarding statin therapy after PCI using intracoronary stenting is quite limited relative to post-PCI studies involving the use of statins after balloon angioplasty. Given this paucity of data in patients undergoing intracoronary stenting, we conducted this trial to determine whether lipid levels relate to in-stent restenosis and whether lipid-lowering therapy using statins can prevent or delay the process of clinically significant restenosis after PCI using a bare metallic stent.

From the Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia (SL, MFE-C, ADP, EV, EA, AZ), and the Department of Biochemistry, Medical School of Athens, Athens, Greece (AT).

Submitted for publication October 19, 2005; accepted for publication November 12, 2005.

Correspondence: Stamatios Lerakis, MD, Associate Professor of Medicine (Cardiology), Emory University School of Medicine, 1365A Clifton Road NE, Suite AT- 303, Atlanta, GA 30322 (E-mail: stam_lerakis@emoryhealthcare.org).

Table 1. Cholesterol Levels in Group I and II

Lipid Profile	Group I (n = 31)	Group II (n = 72)	*P*-value
Total cholesterol	169 ± 22	236 ± 48	< 0.0001
LDL cholesterol	85 ± 16	142 ± 34	< 0.0001
HDL cholesterol	42 ± 19	41 ± 11	0.8349
Triglycerides	144 ± 95	161 ± 92	0.4827

Methods

Study Population

One hundred thirty-six patients underwent single coronary Palmaz-Schatz stenting from June 1995 to June 1997 in our institution. All these patients were followed for at least 9 months (mean, 392 ± 148 days) for major adverse cardiac event (MACE). We defined MACE as the occurrence of death, the occurrence of myocardial infarction, or the need for target lesion revascularization with percutaneous transluminal coronary angioplasty and/or with coronary artery bypass grafting (CABG) and/or with restenting.

Lipid Profile

From this cohort of patients, 103 had at least one lipid parameter from the lipid profile (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides [TGs]) evaluated within 2 months from the date of the procedure. Patients who received the stent because of an acute myocardial infarction (MI) were included in our study only if their lipid profile was evaluated before the acute MI or at least 6 weeks after the date of the MI. Patients with TG levels above 500 had both the TG and LDL levels excluded from the statistical analysis. Patients were divided into Group I (n = 31) patients with normal lipid levels and Group II (n = 72) patients with elevated lipid levels (hyperlipidemic) (Table 1). Baseline clinical demographics obtained from hospital charts and angiographic data obtained from cardiac catheterization records are shown in Table 2.

All follow-up data and data on major adverse cardiac events were obtained from examination of hospital and outpatient clinic charts. All cineangiograms were reviewed and quantitative coronary angiography was performed and used to measure all lesions before and after PCI. All patients were followed for at least 9 months (mean, 392 ±148 days) for MACE.

Definitions

The American College of Cardiology and American Heart Association lesion classification system was used to objectively describe each lesion. Each lesion was scored based on morphology and characterized as type A, B, or C as described elsewhere.[12] MACE was defined as the occurrence of death, MI, or need for target lesion revascularization with balloon angioplasty alone and/or restenting and/or CABG. Patients included in the study had at least one lipid parameter from an available fasting lipid profile. When all parameters of the lipid profile were available, the patient was considered hyperlipidemic when LDL cholesterol was greater than 100 mg/dL. Also, hyperlipidemic patients were considered those with total cholesterol equal to or greater than 200 mg/dL when that was the only cholesterol level available in the lipid profile. Only the total cholesterol level was taken in to account for patients with TG levels above 500 mg/dL.

Statistical Analysis

Continuous variables were compared by the student *t* test and categorical variables by the χ^2 or Fischer exact test. Data are expressed as the mean value ± SD, unless otherwise specified. Significance was defined as a value $P < 0.05$. Statistical analysis was performed with SPSS for Windows (SPSS, Chicago, Illinois).

Results

There were 103 patients who had one at least parameter from the lipid profile. The lipid parameters in Group I (normal lipid profile) and Group II (hyperlipidemic) are shown in Table 1. As shown in Table 2, there was no difference in clinical demographics, angiographic lesion characteristics, or post-PCI luminal diameters noted in the stented segments between the two groups.

During the 9-month follow-up period, there was no significant difference in the MACE rates seen between Groups I and II (22.6% versus 20.8%, P = 0.8), irrespective also of the use of statin therapy in these two groups.

Hyperlipidemic patients in our study were more likely to be on statin therapy, as compared with patients with normal lipid profile (61.1% versus 29%, P = 0.0028).

No differences were seen in the baseline lipid profiles between the patients who had a MACE during the follow-up period versus those who did not (Table 3)

From this cohort of 103 patients, 53 patients were on statin therapy with fluvastatin 40 mg a day (Group III) and the other 50 patients (Group IV) were on no antilipid therapy at all. During the follow-up period, no difference was seen in the incidence of MACE between Groups III and IV (20.8% versus 22%; P = 0.8).

Discussion

In-stent restenosis has unique features that differentiate it from atherosclerosis, despite some similarities. Restenosis occurs as a result of mechanical injury to the intima resulting in neointimal formation. Neointima is formed by smooth muscle cell migration and proliferation stimulated by inflammatory mediators released in response to mechanical stretching of the vessel.[12] Hence, decreasing restenosis should focus on inhibiting smooth muscle migration and proliferation to decrease neointimal formation, which is the mechanism of action of the newer drug-coated stents. Statins, through their anti-inflammatory effect,[13] a characteristic of this drug class that is beyond lipid-lowering, could conceivably reduce neointimal formation. Moreover, reducing LDL, an atherogenic and thrombotic particle,