

The Effects of Lipid-Lowering Therapy on Graft Patency in Coronary Bypass Surgery Patients

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ABSTRACT

Background. Our aim was to investigate the effects of lipid-lowering treatment (LLT) on graft patency in coronary artery bypass grafting (CABG) patients.

Methods. A total of 209 CABG patients (95 men, 45%) with a total cholesterol level above 200 mg/dL and a low-density lipoprotein level above 100 mg/dL were included. Patients were divided into 2 groups on the basis of administration of LLT after CABG: group 1 received LLT after the operation (those patients undergoing operations after 1998, n = 102, 49% male) and group 2 did not receive LLT after the operation (those patients undergoing operations between 1992 and 1998, n = 107, 42% male). Median duration of follow-up was 5.2 years. Follow-up angiography could be obtained in 108 (52%) patients (56 in group 1, 52 in group 2).

Results. There was a 42% reduction in ischemic events and deaths in group 1, and 60% of these patients had a symptom-free or event-free period for 6 years. The 5-year graft patency for left internal mammary artery-to-left anterior descending artery grafts in group 1 was 95%, and the corresponding figure was 90% in group 2. Right coronary artery-to-saphenous vein graft patency was 66% for group 1 and 30% for group 2. Circumflex artery-to-saphenous vein patency rate was 59% for group 1 and 53% for group 2. A higher graft patency was found in group 1 as a whole.

Conclusion. Results of this retrospective study support the fact that LLT provides a higher graft patency for CABG patients.

INTRODUCTION

Cardiovascular diseases, stroke, and peripheral arterial diseases are leading causes of death all over the world [WHO

2002; AHA 2003]. The World Health Organization reported 7.2 million deaths in 2001 [WHO 2002]. Dyslipidemia is the term used for abnormal plasma lipid levels. High levels of total cholesterol (TC), low-density lipoprotein (LDL-C), lipoprotein a, triglyceride (TG), and low high-density lipoprotein (HDL-C), either individually or in combination, are characteristic for dyslipidemic disorders.

In the United States, half of the population has dyslipidemia, which is a modifiable risk factor of atherosclerosis. Adequate treatment of this disorder prevents and reduces the risk for cardiac death, nonfatal myocardial infarction, stroke, revascularization procedures, and peripheral artery diseases by 25% to 80%. Although the favorable effects of lipid-lowering treatment (LLT) on mortality have already been established, thousands of deaths still occur every year due to inadequate medical treatment [4S Study Group 1994].

Twenty years ago there was doubt regarding the association between LLT with atherosclerosis and coronary heart disease; however, in 1994, the 4S study proved the beneficial effects of LLT on mortality in coronary heart disease patients without previous bypass surgery [4S Study Group 1994]. After this study, many other clinical investigations have confirmed the beneficial effects of LLT on major coronary events and mortality [WHO 1980; Brown 1990; Huttunen 1991; Ravnskov 1992; Pitt 1995; Frick 1997; PCABG Trial Investigators 1997; Lewis 1998; LIPID Study Group 1998; Pedersen 1998; WOSCOPS Study Group 1998; Haim 1999; Rubins 1999; HPS Collaborative Group 2002; Shepherd 2002; Sever 2003].

One of the largest cholesterol-lowering treatment studies conducted with coronary artery bypass surgery (CABG) patients was the Cholesterol Lowering Atherosclerosis Study 1 (CLAS 1) and the long-term follow-up of the same study was CLAS 2 [Blankenhorn 1987; Cashin-Hemphill 1990].

We aim to report the results of our CABG patients with or without postoperative LLT. Groups were followed for a median duration of 5.2 years and compared in terms of graft patency assessed with coronary angiography.

MATERIALS AND METHODS

Two hundred nine CABG patients (45% male) were divided into 2 groups: group 1 was composed of patients who had undergone operations after 1998 (n = 102, 49% male),

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and patients in group 2 had undergone operations between 1992 and 1998 (n = 107, 42% male).

All patients had a complete physical examination and laboratory tests for renal functions, liver functions, and lipid profile. All blood samples were obtained after at least 10 to 12 hours of fasting and serum was extracted and stored at -40°C . Serum TC and TG levels were measured by the enzymatic method using both an RA-1000 and RA-XT autoanalyzer (Technicon, Saskatoon, SK, Canada). HDL serum levels were measured by the magnesium chloride phospho tungstic acid debris method. LDL levels were then calculated by Friedewald formula ($\text{LDL-C} = [\text{TC}] - [\text{TG}/5 + \text{HDL-C}]$) for cases with TG levels < 400 mg/dL [Friedewald 1972].

All patients had baseline coronary angiography prior to CABG and were divided on the basis of TC levels (>200 mg/dL), LDL levels (>100), and antilipidemic treatment. After CABG surgery, antilipidemic treatment was given in group 1 and was not given in group 2. Both groups had a baseline and a follow-up coronary angiography. Each angiography pair was reviewed by cardiologists blind to the treatment. Strict criteria for atherosclerotic progression could not be employed due to different technical standards of previous and current angiograms. Quantitative assessment of stenosis was not possible in early angiographies. The presence of atherosclerotic progression was decided on by the relevant cardiologist using his clinical experience. Also, graft patency at baseline and at follow-up was compared between groups. Median duration of follow-up was 5.2 years.

Exclusion criteria were as follows: symptomatic congestive heart failure and low left ventricular ejection fraction ($<25\%$), familial hypercholesterolemia, chronic liver disease, being overweight, use of certain drugs (immunosuppressives, corticosteroids, androgens, progestins, and estrogens), allergy to LLT, and radial artery bypass conduits at any position. Both groups were similar in terms of age, race and sex distribution, body mass index, number of grafts (single or double bypass), and type and location of conduit (left internal mammary artery-to-left anterior descending artery [LIMA-LAD], saphenous vein-to-right coronary artery [RCA] or to circumflex coronary artery [Cx]).

The following clinical coronary events were recorded: requirement for revascularization due to recurrence or worsening of angina pectoris (percutaneous transluminal coronary angioplasty [PTCA], CABG), nonfatal acute myocardial infarction (MI), and coronary death.

Hospital and municipality records were reviewed for the confirmation of all subject-reported coronary events. Cause of death was confirmed by hospital records or municipality reports, which are reliable certificates.

All patients were advised to stop cigarette smoking and to change their lifestyle and eating habits. The National Cholesterol Education adult treatment group recommends LDL levels to be lower than 100 mg/dL in CAD. All patients received 10, 20, or 40 mg of pravastatin adjusted according to their LDL cholesterol levels. Patients with a LDL level between 110 to 150 mg/dL received 10 mg, patients with levels between 150 to 200 mg/dL received 20 mg, and patients with a LDL ≥ 200 mg/dL received 40 mg of pravastatin. All 3 subset groups were regarded as a statin treatment group.

Statistical Analysis

Values of selected variables were summarized by standard descriptive statistics and expressed as mean \pm standard deviation. Independent samples *t* test (Mann-Whitney U test when Levene test is significant) and chi-squared test were used to compare continuous and categorical variables between groups, respectively. Statistical significance was defined by a *P* value $< .05$. The SPSS 11.5 program (Chicago, IL, USA) for Windows was used for the entire statistical work up.

RESULTS

Ninety-four percent of group 1 patients (n = 96) were able to complete statin therapy and 6% (n = 6) discontinued due to myopathy, elevated liver enzymes, gastrointestinal side effects, or skin rash. Myopathy (9%, n = 19) and elevation of liver enzymes (15%, n = 31) were the most frequent adverse effects of LLT in patients who continued treatment. During the follow-up period, we were able to follow 89% of the patients in group 2 (n = 95). Twelve cases (11%) could not be followed. Overall, follow-up coronary angiography could be performed in 108 (52%) CABG patients (56 in group 1, 52 in group 2).

The major regression of lipid levels in group 1 was started by the beginning of the 3rd month ($P < .05$) and reached a peak decline at the 6th month. The results of the lipid levels are given in Table 1.

When LIMA-LAD bypass grafts were considered, the 5-year graft patency rate was 95% and 90% in group 1 and group 2, respectively. Graft patency rate for saphenous vein-RCA grafts were 66% in group 1 and 30% in group 2. The Cx-saphenous vein patency rates were 60% for group 1 and 53% for group 2. When saphenous vein-RCA and saphenous vein-Cx grafts were compared, grafts to RCA showed a higher patency rate ($P < .005$). Overall, a higher graft patency rate was found in group 1 ($P < .005$).

In patients who were treated with LLT to maintain LDL-C levels within the recommended range (group 1), 21% (12/56)

Table 1. Lipid Levels of Group 1 during the First 6 Months*

Mg/dL	Before CABG	1st Month	3rd Month	6th Month
Total cholesterol	230 \pm 21.5	227.48 \pm 17.89	211.74 \pm 15.39	183.74 \pm 13.19
LDL cholesterol	148 \pm 13.1	147.56 \pm 23.34	132.97 \pm 23.41	106.28 \pm 21.62
Triglycerides	290 \pm 24.9	279.74 \pm 47.19	249.54 \pm 41.95	216.57 \pm 39.88
HDL cholesterol	29 \pm 2.3	30.28 \pm 3.26	33.14 \pm 3.71	38.40 \pm 3.28

*CABG indicates coronary artery bypass grafting; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

of patients showed atherosclerotic progression; however, the corresponding figure was 85% (44/52) in group 2.

In the present study, the formation of new lesions in bypass grafts has been found to be a precursor of poor clinical outcome. New lesions formed both in native and coronary bypass grafts in group 2 resulted in a higher rate of adverse coronary events and deaths (95% CI = 1.014-1.022, OR = 0.2, $r = 0.39$). When stratified by lesion location, angiographic presence of progression either in native vessels or bypass grafts was found to be predictive of clinical coronary events, even after new lesions were excluded ($r = 0.32$; $P = .004$).

There was a 42% reduction in ischemic events and deaths in group 1 compared to group 2 ($r = 0.92$; $P < .0005$), and 86% of group 1 patients had a symptom- or event-free period of 5.2 years. We have found no reduction in ischemic events and deaths in group 2 ($r = 1.4$; $P = .6$).

DISCUSSION

In the present study, LLT has provided a better 5-year graft patency rate in CABG patients. Hypercholesterolemia, particularly elevated levels of LDL-C, is a well-established risk factor for coronary artery disease (CAD), and lowering LDL-C will decrease the CAD risk. Patients should receive LLT to achieve and maintain LDL-C levels within the National Cholesterol Education Program's (NCEP) recommended target of less than or equal to 100 mg/dL (less than or equal to 2.59 mmol/L) [4S Study Group 1994; WOSCOPS Study Group 1998]. The groups' lesion types are shown in Table 2; baseline findings were similar ($P = .04$).

During the 5.2-year follow-up period, LLT provided higher graft patency rates and lower incidence of adverse coronary events in CABG patients, regardless of the atherosclerotic lesion types. The graft patency rates were similar to those previously reported, and the adverse coronary events were seen mostly in group 2 [Pitt 1993; Crouse 1995; REGRESS Study Group 1995; Shepherd 1995; Azen 1996; Frank 1998]. Numerous anti-atherosclerotic trials using coronary angiography to evaluate graft patency or progression of atherosclerotic lesions (on native vessel or graft) have reported the beneficial effects and the results of LLT, cholesterol-lowering diet, and other lifestyle changes [Ravnskov 1992; REGRESS Study Group 1995; Shepherd 2002]. Our study has clearly shown the beneficial effects of LLT among the CABG patients in terms of graft patency rate as well as adverse coronary events and deaths.

Subjects with greater mild/moderate lesion progression at 2 years are at increased risk for future clinical coronary events [WHO 1980; Huttunen 1991; Ravnskov 1992]. Although

severe lesions are more likely to progress to occlusion than mild/moderate lesions, clinical coronary events more frequently occur as a consequence of acute occlusion of mild/moderate lesions. This better outcome after occlusion may be due to the presence of more effective collateral circulation or previous CABG operation in patients with severe lesions. In both groups, the lesions were mostly classified as type A and B in our patients. Although there was a significant reduction in clinical coronary events with LLT in CABG patients, we were unable to determine which specific lesions regressed and what causes this reduction, because angiography was not performed at the time of coronary events. However, the Familial Atherosclerosis Treatment Study (FATS) demonstrated that mild/moderate lesion stability provided by LDL-C lowering significantly reduced on-trial clinical coronary events [Brown 1990].

Study Limitations

Although this study has included large number of CABG patients, it still has several limitations. Firstly, our study has a retrospective design, and group 1 and group 2 patients received treatment at 2 chronologically different time periods, which may cause a bias in favor of group 1. Not only was the technical quality of previous angiograms lower, but group 2 patients might also have received better care due to advancements in treatment. Secondly, follow-up coronary angiography could be obtained in only 52% ($n = 108$) of both group 1 and 2 cases. This limitation might have led to the underdiagnosis of clinically silent CAD in patients who did not have coronary angiography. The main goal of this study was to assess the beneficial effect of LLT on graft patency rates in CABG patients rather than to assess the incidence of adverse coronary events and deaths.

CONCLUSION

LLT provides a higher graft patency rate in CABG patients, therefore we suggest that LLT should be started after surgery for all CABG patients and this therapy should be a complementary rather than a competitive strategy (PTCA, CABG, etc) for the treatment of CAD. The benefits of TC and LDL-C lowering in CABG patients need further investigation in multicenter studies.

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Table 2. Type of Lesions in Group 1 and Group 2 (Preoperative)

Type of Lesion	Group 1 (n = 102)	Group 2 (n = 107)
Type A	65% (n = 66)	66% (n = 71)
Type B	31% (n = 32)	29% (n = 31)
Type C	4% (n = 4)	5% (n = 5)

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