Circulation

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Simvastatin Initiated Early After Heart Transplantation
8-Year Prospective Experience

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Background—Randomized clinical trials have demonstrated that the use of statins in heart transplant patients lowers cholesterol levels and significantly reduces mortality and the development of transplant vasculopathy. The aim of the present study was to test these effects and the safety of statin therapy over an 8-year period.

Methods and Results—In 1991, a prospective, randomized, unmasked study was initiated to compare the efficacy of simvastatin, started on the fourth postoperative day (n=35), with that of dietary therapy alone (n=37). Because of significantly improved survival and a lower incidence of transplant vasculopathy, most patients in both groups received statins as open-label prescriptions after 4 years. After 8 years, the Kaplan-Meier survival rate was 88.6% in the simvastatin group versus 59.5% in the control group ($P<0.006$ by log rank; hazard ratio, 0.24; 95% CI, 0.08 to 0.71). Deaths in the simvastatin and control groups were due to transplant vasculopathy (1 versus 4; $P<0.2$), severe transplant rejection (1 versus 5; $P<0.1$), malignancies (0 versus 3; $P<0.1$), and other causes (2 versus 3; $P<0.7$). The incidence of transplant vasculopathy confirmed by angiography was 24.4% in the simvastatin group versus 54.7% in the control group ($P<0.02$ by log rank). There was no difference in organ function between the 2 groups. No severe adverse effects of the therapy were observed up to the end of the 8-year observation period.

Conclusions—Simvastatin therapy initiated early after heart transplantation leads to significantly better 8-year survival rates and a significantly lower incidence of transplant vasculopathy without impairment of organ function or severe adverse effects. (***Circulation***. 2003;107:93-97.)

Key Words: cholesterol ■ transplantation ■ simvastatin

The development of transplant vasculopathy remains the most daunting long-term complication of heart transplantation surgery, with an annual incidence rate of 5% to 10%.[1–3] The prognosis of heart transplant recipients is largely determined by the occurrence of transplant vasculopathy: After the first postoperative year, transplant vasculopathy becomes increasingly important as a cause of death.[4,5] Qualitative and quantitative coronary angiographic studies and intracoronary ultrasound studies have shown that the process of vascular constriction after heart transplantation occurs in nearly all coronary vessel sections.[6–8] The causes of transplant vasculopathy are multifactorial; transplant rejections, viral infections, and surgical and metabolic causes are all suspected.[3–5] The preventive use of the calcium antagonist diltiazem proved promising in a prospective, randomized study.[9] Consistent treatment with diltiazem resulted in significantly less constriction of coronary lumina than in untreated heart transplant recipients, as assessed by qualitative coronary angiography. However, no improvement in the long-term survival rate of the patients was demonstrated in this study.[3,9] Another promising approach to the prevention of transplant vasculopathy is the use of the statins pravastatin and simvastatin.[7,8] Both these drugs result in significantly lower cholesterol levels, as well as significantly improved survival rates, significantly fewer severe transplant rejections, and a significantly lower incidence of transplant vasculopathy.

In our prospective, randomized simvastatin study, we evaluated whether the aforementioned positive effects of simvastatin therapy initiated immediately after heart transplantation continued over the 8-year observation period and whether the treatment is sufficiently safe for these patients.

Methods

The design of the simvastatin study has been described elsewhere.[8] A total of 72 patients who had undergone orthotopic heart transplantation were randomly assigned to a treatment and a control group.

Baseline Characteristics of the Patients in Both Groups

	Simvastatin (n=35)	Control (n=37)
Recipient age, y	49±11.5	46.8±14.3
Donor age, y	30.0±11.1	33.9±10.4
Duration of ischemia, min	175±62	180±52
Male/female sex, n	30/5	34/3
Coronary heart disease before transplantation, %	28	26
Hypercholesterolemia before transplantation, %	37	32
Diabetes, %	11	8

Values are mean±SD unless otherwise indicated.

Both groups were put on a strict low-cholesterol diet (American Heart Association step II diet; cholesterol <200 mg daily). In the intervention group, simvastatin therapy at a dosage of 5 mg daily was initiated on the fourth postoperative day. The therapeutic target in this group was a low-density lipoprotein (LDL) level of <120 mg/dL. A dosage adjustment up to 20 mg simvastatin daily was undertaken 4 to 6 weeks after transplantation depending on the LDL level. All the patients received standard triple immunosuppression therapy consisting of cyclosporin A (blood level >500 ng/mL), azathioprine (1 mg/kg body weight), and prednisolone (0.1 mg/kg body weight). After transplantation, no antibody induction treatment was used. In view of the significantly better results in the intervention group, the regimen in the control group was changed after year 4 of the study, and these patients were also offered simvastatin therapy in a dosage of 5 to 20 mg daily; the therapeutic target was again an LDL cholesterol level of <120 mg/dL. This was undertaken after evaluation by the ethics review board of the University of Munich. The patients originally assigned to the simvastatin group continued to receive this treatment. Over a total observation period of 8 years, the survival rates, the incidence of transplant vasculopathy in the coronary angiogram, the incidence and severity of transplant rejections, cholesterol and LDL cholesterol levels, hepatic and renal function, and adverse effects of the statin therapy were observed and evaluated in both groups on the basis of the original randomization (intention-to-treat approach). Coronary angiography was performed in the first month after transplantation to establish the baseline coronary status, and it was repeated at yearly intervals in all patients. Transplant vasculopathy was defined as any angiographically demonstrated new stenosis of >50% or new distal obliterative changes. Transplant rejections were diagnosed by endomyocardial biopsy and classified according to the system of the International Society for Lung and Heart Transplantation as mild (grade IA or IB), focal moderate (grade II), multifocal moderate (grade IIIA), or diffuse borderline severe (grade IIIB).

Statistics

The total mortality rate and the time to the occurrence of transplant vasculopathy were tested for differences between the treatments in the Cox proportional hazard models (log-rank test). The proportional hazards conditions were met. All other data were subjected to t or χ^2 tests. The significance level was set at $P<0.05$.

Results

At the time of randomization, there were no significant differences between the 2 study groups in terms of sociodemographic or clinical characteristics (Table). Blood cyclosporine levels in the 2 groups did not differ significantly during the observation period. Acceptance of the pharmacological cholesterol-lowering therapy was satisfactory in both
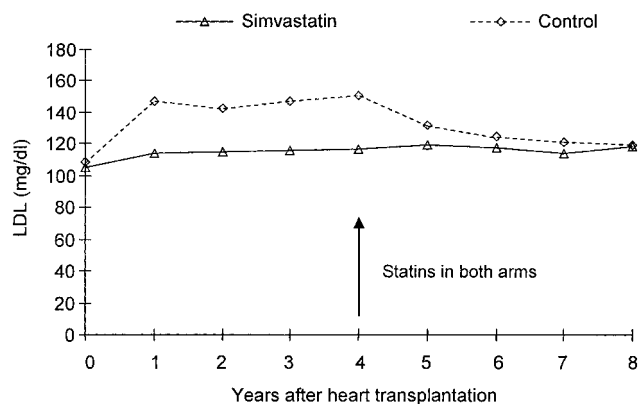

Figure 1. The 8-year LDL cholesterol profile in both groups (to convert values to mmol/L, multiply by 0.02586).

groups: from year 5 on, patients of the intervention group regularly took simvastatin (77.4%), pravastatin (9.7%), cerivastatin (6.5%), atorvastatin (3.2%), or no statin (3.2%), and patients of the control group regularly took simvastatin (59.2%), pravastatin (13.6%), atorvastatin (4.5%), lovastatin (4.5%), or no statin (18.2%).

LDL Cholesterol

In the simvastatin group, the LDL cholesterol levels remained <120 mg/dL throughout the 8-year observation period (mean, 116.2±18 mg/dL). In the control group, the levels were significantly higher (156±24 mg/dL; $P<0.002$). After year 4, when cholesterol-lowering therapy was introduced in the control group as well, the LDL cholesterol values fell to 118±18 mg/dL, which was within the defined target range. The difference between the groups was no longer significant ($P<0.13$; Figure 1).

Survival

Eight years after the start of the study, 31 patients were still alive in the simvastatin group (88.6%) versus 22 patients in the control group (59.5%). The difference between the 2 groups was highly significant ($P<0.006$ by log rank; hazard ratio, 0.24; 95% confidence interval [CI], 0.08 to 0.71). The causes of death observed in the simvastatin group were severe transplant vasculopathy in one case, severe transplant rejection with graft failure in one case, and pneumonia in 2 cases. In the control group, by contrast, there were 4 cases of severe transplant vasculopathy, 5 cases of severe transplant rejection, 3 cases of malignant tumors, 2 cases of pneumonia, and one case of severe anaphylaxis. A total of 4 patients in the intervention group died compared with 15 patients in the control group (Figure 2).

Transplant Vasculopathy

In the fourth postoperative year, the difference between the 2 groups was already significant: 16.2% of the initially treated patients versus 42.3% of the initially untreated control patients developed transplant vasculopathy. An impressive continuation of this development was observed after year 8 of the study. Whereas 24.4% of the initially treated patients devel-
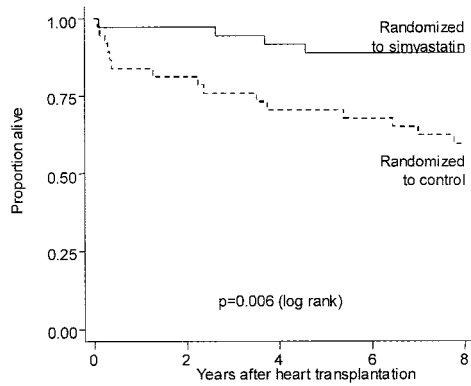
Figure 2. Survival curves for both study groups.

Figure 4. Mean 8-year creatinine kinase (CK) profiles in both groups.

oped transplant vasculopathy, the corresponding figure in the control group was 54.7% (*P*<0.02 by log rank; hazard ratio, 0.35, 95% CI, 0.15 to 0.83; Figure 3).

Transplant Rejections

Transplant rejections were most frequently observed in the first postoperative year. There were no significant intergroup differences in terms of the number of rejections per patient. However, the more frequent occurrence of severe transplant rejection accompanied by graft failure (grade IIB) in the control group up to the fourth postoperative year was noteworthy. Only one patient in the intervention group (2.8%) died as the result of refractory transplant rejection compared with 5 patients in the control group (13.5%). However, this difference was not statistically significant (*P*<0.1). In the course of the final 4 years of observation, no further transplant rejections occurred in either study group.

Organ Function and Adverse Effects

Analysis of the renal function parameters showed no significant differences between the simvastatin and control patients
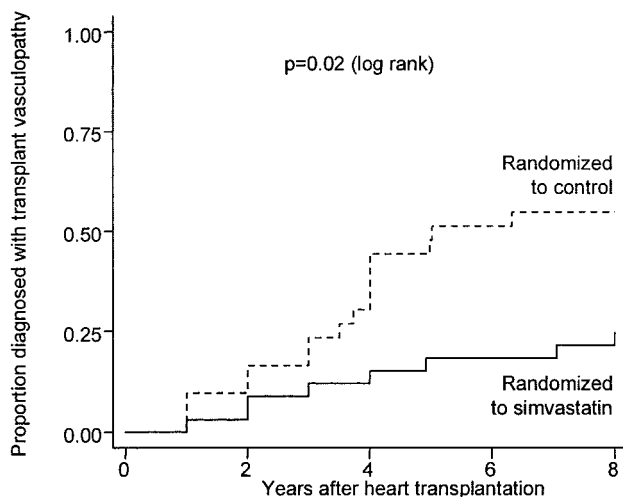

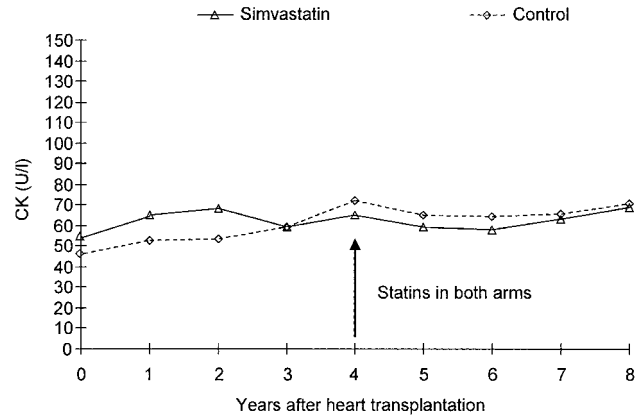Figure 3. Time to the occurrence of transplant vasculopathy for both groups.

during the 8-year observation period. Nor were there any significant differences between the 2 groups in terms of liver function. The potential muscular side effects of statin therapy merited special attention. The measured levels of creatinine kinase did not differ significantly in the long term between the initial intervention group and the initial control group (Figure 4). Creatinine kinase elevations >100 U/L were observed in 12 patients in the intervention group versus 10 patients in the control group. In every case, the observed elevations were reversible and occurred after the muscular activity of the patient concerned. No severe adverse effects of the therapy occurred in either group over the entire observation period. In particular, no case of rhabdomyolysis was observed.

Discussion

Transplant vasculopathy remains one of the most severe complications of heart transplantation. Whereas the 1-year survival rate is frequently reported to be >90%, the long-term success of heart transplantation is significantly limited by the development of coronary sclerosis.[3,4] The results of the present 8-year study show that simvastatin treatment initiated in the early phase after heart transplantation lowers levels of cholesterol, particularly LDL cholesterol, safely and effectively, significantly reduces the development of transplant vasculopathy, and significantly improves the long-term survival prognosis of patients.

As far as an explanation for the good results is concerned, the consistent and effective lowering of cholesterol levels played a decisive role. Large-scale randomized studies have recently shown once again that consistent treatment with simvastatin leads to less progression of coronary heart disease, significantly fewer cardiac events, and a significantly improved overall survival rate.[10–12] These positive effects are also observed in heart transplant patients.[7,8,13–15]

However, for heart transplant patients, it seems crucial that simvastatin therapy be initiated as early as possible after transplantation. As mentioned earlier, the control group patients also received statins, mainly simvastatin, after year 4 of the study. In this group, cholesterol and LDL cholesterol levels also fell significantly. However, to date, no positive

effect on the development of transplant vasculopathy has been demonstrated in this group. This observation is in agreement with those of other authors, who achieved a significant reduction in cholesterol in a comparable patient population in whom statin therapy was initiated an average of 24 months after heart transplantation with no reduction in the incidence of transplant vasculopathy.[13]

In addition to the cholesterol-lowering activity of simvastatin, there are also other biological mechanisms that may figure prominently in the development of transplant vasculopathy. Thus, simvastatin inhibits the proliferation of smooth muscle cells, an important process in the pathogenesis of atherosclerotic lesions.[16] This effect is explained by the fact that, in addition to inhibiting cholesterol biosynthesis, simvastatin also reduces the production of mevalonate and associated isoprenoids, farnesylpyrophosphate and geranylpyrophosphate. As a result, intracellular signal transduction and, consequently, the protein synthesis required for growth processes are inhibited.[17] In addition, statins have a direct influence on the expression of genes for growth factors that are essential for the proliferation of smooth muscle cells.[17,18] Moreover, simvastatin has been shown to have a direct influence on the gene expression of endothelin-1 in cultivated endothelial cells, leading to improved endothelial function and thus protecting against atherosclerosis.[19] Another direct positive effect of simvastatin in the atherogenesis process that has recently been described is that it reduces monocyte adhesion to endothelial cells, one of the initial steps in the development of atherosclerotic plaques.[20] These reported effects of simvastatin may have been additive or multiplicative in their contribution to the finding that transplant vasculopathy occurred less frequently in our early intervention group.

The significant improvement in long-term survival over the 8-year period was due not only to a decreased number of transplant vasculopathy–related deaths but also to a reduced number of severe transplant rejections with graft failure. Although transplant rejections as a whole were equally distributed between the 2 study groups, more deaths due to severe transplant rejection occurred in the control group. This is an interesting phenomenon, because statins alone exhibit no immunosuppressive activity in vivo. In a large-scale study in which coronary patients received statin therapy, no changes in the number or function of T lymphocytes, B-lymphocytes, or natural killer cells were observed.[21]

In the presence of the immunosuppressant cyclosporin A, however, statins seem to develop immunomodulating effects. Thus, statins were shown to result in reduced natural killer cell activity in vitro.[22,23] In addition, T-cell proliferation and T lymphocyte cytotoxicity were inhibited.[24] Other reported immunomodulating effects of statins in the presence of cyclosporin A include suppression of T-cell responses, reduction of chemokine synthesis by mononuclear cells in the peripheral bloodstream, and inhibition of the expression of MHC-II genes.[25,26] The underlying mechanism of these effects remains uncertain. However, it is conceivable that as a result of statin-induced LDL receptor activation, more LDL-bound cyclosporin A becomes available intracellu-

larly and inhibits immunologically competent cells more strongly.[8] However, this is a working hypothesis that has yet to be corroborated. No adverse effects of long-term treatment with simvastatin in heart recipients were noted over the entire 8-year course of the study, underscoring the good tolerance and safety of the therapy in this patient group.

In conclusion, postoperative therapy with simvastatin initiated early after heart transplantation led to effective and safe reduction of cholesterol levels over a period of 8 years. The occurrence of severe transplant rejections with graft failure was reduced, and the development of transplant vasculopathy was significantly reduced, resulting in a significant improvement in survival rates. Serious long-term adverse effects of the treatment are not expected.

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