Drugs 2004; 64 (10): 1053-1068
0012-6667/04/0010-1053/$34.00/0

Management of Hyperlipidaemia Associated with Heart Transplantation

Klaus Wenke

Division of Cardiac Surgery, Hospital Munich-Bogenhausen, Munich, Germany

Contents

Abstract

The past 20 years have seen considerable advances in the field of organ transplantation that have together led to a notable increase in survival rates and a reduction in postoperative morbidity of transplant recipients. However, these advances have been accompanied by the appearance of other complications of transplantation, such as post-transplant hyperlipidaemia, hypertension and graft coronary vasculopathy (GCV). GCV is an accelerated form of atherosclerosis in transplanted hearts that has proven to be one of the most important late complications of heart transplantation and is the single most limiting factor for long-term survival.

The most important factors favouring the development of hyperlipidaemia after heart transplantation are inappropriate diet in combination with reduced physical activity, adverse effects of immunosuppressive therapy (ciclosporin [cyclosporin], corticosteroids) and polygenic hypercholesterolaemia in combination with ischaemic cardiomyopathy.

The treatment of hyperlipidaemia in heart transplant recipients results in a variety of complications and side effects. In particular, interactions between lipid-lowering drugs and immunosuppressive therapy have been observed. Early attempts at treatment with bile acid binding agents and nicotinic acid derivatives often proved insufficiently effective, and led to unacceptable adverse effects and

significant disturbances of ciclosporin metabolism. Fibric acid derivatives provided moderate reductions in triglyceride and total cholesterol levels that were mostly – with the exception of gemfibrozil – accompanied by significant impairment of renal function. Probucol achieved only an unsatisfactory reduction in low-density lipoprotein (LDL) cholesterol. Omega-3 fatty acids lower cholesterol levels and improve endothelial function in heart transplant recipients; however, the significance of these effects is still under discussion. As in the general patient population, use of HMG-CoA reductase inhibitors (statins) achieved significant reductions in cholesterol levels. Use of these substances has resulted in significantly extended long-term survival times, significantly less GCV and fewer severe graft rejections. Selective cholesterol absorption inhibitors, administered with or without statins, could provide another treatment option for heart transplant patients with hypercholesterolaemia. In severe familial hypercholesterolaemia, which is rarely observed in heart transplant recipients, treatment with statins can be combined with extracorporeal cholesterol elimination procedures such as heparin induced extracorporeal LDL cholesterol precipitation (HELP). HELP enables total cholesterol levels to be kept within any desired target range, and has been used successfully and without adverse effects in heart transplant recipients.

Over the past two decades improvements in immunosuppressive therapy, infection prophylaxis and therapy, and surgical management have led to a considerable improvement in survival rates and to a reduction in early morbidity after heart transplantation. However, these advances have been accompanied by the appearance of a multiplicity of other and previously unknown complications.[1] One such problem is post-transplant hyperlipidaemia. This affects the long-term outlook not only of heart but also of renal and liver transplant recipients.[2-5] Many large-scale clinical studies have shown a correlation between elevated lipid levels and the development of atherosclerosis.[6-8] It seems reasonable to assume that elevated lipid levels increase the risk for cardiovascular disease in transplant recipients just as they do in the general population.[9-11]

It is also assumed that, together with other factors, elevated lipid levels hasten the development of graft coronary vasculopathy (GCV), an accelerated form of coronary artery sclerosis in the transplanted heart which, with an annual incidence of 10%, is the most common cause of late death after heart transplantation.[12-15]

Atherosclerotic changes in nontransplanted blood vessels are another possible complication of hypercholesterolaemia, as suggested by the fact that peripheral vascular disease develops sooner or later in 10% of heart transplant recipients.[16]

This article summarises the mechanisms, clinical associations and ways of treating hyperlipidaemia in heart transplant recipients.

1. Hyperlipidaemia After Heart Transplantation

Pathological changes in lipid parameters can be found in about 60–80% of heart transplant recipients given standard triple immunosuppression consisting of ciclosporin (cyclosporin), azathioprine and methylprednisolone.[17-19] Many studies on such transplant patients have found that plasma levels of total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), apolipoprotein B and triglycerides increase between 3 and 12 months after transplantation.[20] In the longer term, the elevated lipoprotein fractions show a gradual fall, although even then they remain above their respective normal range. Conflicting results have been obtained regarding high-density lipoprotein (HDL) cholesterol levels. This lipoprotein fraction appears not to be significantly influenced by transplantation.[21] Lipoprotein (a) [Lp(a)] levels are re-

duced after transplantation in 40% of patients.[18] Another study found elevated Lp(a) levels to be an independent risk factor for the development of GCV.[22,23]

Three months after heart transplantation there is a marked increase in total cholesterol to a level about 40% higher than the pretransplant level,[20] while LDL cholesterol increases by about 34% and triglycerides by up to 82%. The lipid levels rise most markedly in the first 3 months and then stabilise at abnormally high values even if systematic dietary measures are observed.

Hyperlipidaemia develops after heart transplantation for a variety of reasons. Some patients, in particular those in whom ischaemic cardiomyopathy and hypercholesterolaemia are present even before transplantation, are genetically predisposed to the condition by polygenic dyslipidaemia.[11] Dietary factors also play a role. Many patients have a low or ideal bodyweight before transplantation. Following transplantation, 50% of patients put on weight as a result of a corticosteroid-induced increase in appetite.[24] A diet high in saturated fat, glucose and calories can contribute to excessive bodyweight. Overweight, in turn, is closely associated with the development of hyperlipidaemia in the general population and, thus, also contributes to the development of hypercholesterolaemia after heart transplantation.[25]

Another important factor in the development of hyperlipidaemia is postoperative immunosuppressive therapy with corticosteroids and ciclosporin.[24,26] Corticosteroids are known to act at various points in lipid metabolism and, thereby, to elevate a number of lipid parameters. One such effect is an increase in the activity of acetyl-coenzyme A (CoA) carboxylase and a consequent elevation of free short-chain fatty acid levels. Another effect is activation of free fatty acid synthesis and a consequent increase in the synthesis of long-chain fatty acids. These processes lead to an increase in hepatic synthesis of VLDL. Hepatic LDL receptor activity is downregulated by corticosteroids. At the same time, activity of HMG-CoA reductase, the key enzyme in cholesterol biosynthesis, is markedly increased. In contrast, lipoprotein lipase activity is inhibited by corticosteroids. These various processes lead to markedly elevated plasma levels of VLDL, increased total cholesterol and triglyceride levels, and a marked reduction in HDL levels.[24] Corticosteroids may also induce insulin resistance with compensatory hyperinsulinaemia. A high prevalence of severe glucose intolerance, hyperinsulinism, hypertriglyceridaemia and hypercholesterolaemia has been reported in heart transplant patients.[27] Insulin is crucial for the regulation of VLDL secretion and catabolism.[28] Insulin resistance enhances VLDL secretion and impedes the removal of triglycerides from VLDL in the circulation. This results in hypertriglyceridaemia and high VLDL levels. Furthermore, the expanded VLDL pool increases the transfer of cholesterol out of HDL and probably out of LDL to VLDL. This in turn leads to low levels of HDL cholesterol and the formation of small cholesterol-depleted LDL. These small dense LDL particles are rich in triglycerides but contain relatively little cholesterol and are not readily cleared by the physiological LDL receptor. On the contrary, they readily undergo oxidative modification and become highly atherogenic. Thus, it has been suggested that the risk associated with hyperinsulinaemia as a marker of insulin resistance is largely explained by lipid abnormalities.[29]

It is now known that ciclosporin also acts at various points in lipid metabolism. Ciclosporin inhibits the enzyme 26-hydrolase, which plays a crucial role in the biosynthesis of bile acids. Ciclosporin directly reduces conversion of cholesterol to bile acids and, thereby, reduces transport of cholesterol to the intestine.[26] Another mode of action of ciclosporin is based upon the affinity of the ciclosporin molecule for LDL receptors. Binding of ciclosporin to these receptors leads to an increased level of LDL cholesterol in peripheral blood.[26] Increased hepatic lipase activity and reduced lipoprotein lipase activity have also been observed in patients receiving ciclosporin. These changes lead to an imbalance between the LDL and VLDL lipoprotein fractions.[4,5]

2. Graft Coronary Vasculopathy

Closely related to the development of hypercholesterolaemia is the development of GCV.[9] GCV is the most important late complication of heart transplantation. It is the main cause of chronic failure of the transplanted heart and makes a significant contribution to patients' long-term morbidity and mortality.[19,20] The incidence of the condition is said to be 5–10% per year and 20–50% by the third postoperative year.[21] Coronary angiography has been shown to underestimate the presence of GCV and, therefore, has not proven to be a sensitive method of diagnosis. The insensitivity of coronary angiography in the diagnosis of GCV, except for significant focal stenoses, has been demonstrated by histopathological studies[30] and by comparison with intracoronary ultrasound.[31] This insensitivity may be due to compensation of severe intimal thickening by vessel-enlarging remodelling. Additionally, in the rare event of homogeneous intimal proliferation there may be no reference vessel segment for detection of luminal narrowing.[32]

In addition to the classical causes of atherosclerosis referred to earlier, various immunological processes have been hypothesised as playing a role in the pathogenesis of GCV.[21,33]

A positive correlation has also been found between high donor age at the time of transplantation and postoperative development of GCV.[34,35] This association has been explained on the basis that the probability of pre-existing coronary disease increases with increasing donor age.

Nevertheless, the precise mechanism by which GCV develops has yet to be elucidated. Much evidence suggests that the initial process is one of endothelial damage mediated by cellular and humoral immune mechanisms in a milieu of additional nonimmunological risk factors.[36,37] Humoral and cellular immune responses to human lymphocyte antigens (HLA) could be responsible for the endothelial damage. A complete HLA-D-related mismatch is regarded as a risk factor for GCV, as is postoperative formation of anti-HLA antibodies.[38] The stimulation of major histocompatibility complex (MHC) class II antigens on endothelial cells induced by activated CD4+ T cells also triggers a cellular immune response. The endothelial cell is a principal determinant of vessel wall function. Normally it inhibits thrombus formation and leucocyte adhesion, regulates the vasomotor function of the vessel and inhibits proliferation of vascular smooth muscle cells (VSMC). Therefore, endothelial damage can disturb any or all of these functions and, thus, predispose to arterial inflammation, thrombosis, vasoconstriction, and growth and migration of VSMC.

Independently of the initial, immunologically mediated, endothelial lesion, the cascade of events triggered in this way results in a physiological and specific inflammatory immune reaction known as a 'response to injury'.[39] A particularly important aspect of this is the fact that activated lymphocytes release interferon-γ, which stimulates synthesis of the intercellular adhesion molecule (ICAM)-1. Adhesion molecules play a crucial role in regulating the interaction between inflammatory cells and the cells of the vessel wall. Adhesion of leucocytes to endothelial cells is a prerequisite for leucocyte transmigration. Demonstration of ICAM-1 expression in the early postoperative phase has been linked to early occurrence of angiographically visible GCV.[40] Macrophages, T cells, endothelial cells and VSMC produce a variety of cytokines and growth factors that cause further progression of the chronic vascular lesion. Eventually the process triggers a repair mechanism that causes migration and proliferation of VSMC of the vessel wall and, thus, narrowing of the vessel lumen.[41]

Immunological risk factors for the development of GCV are now known to include elevated levels of cytotoxic B-cell antibodies, elevated levels of anti-HLA antibodies, increased incidence of acute cellular and humoral rejection, cytomegalovirus infections, sensitisation to monoclonal antibodies, and early and persistent elevation of interleukin-2 receptor levels.[21]

Nonimmunological risk factors for the development of GCV include hyperlipidaemia, recipient age and sex, overweight, ischaemic cardiomyopathy and donor ischaemia time. Hypercholesterolaemia is the

nonimmunological risk factor most frequently present and most constantly correlated with the development of GCV. Histochemical studies of explanted transplanted hearts have shown levels of total cholesterol, cholesterol esters and free cholesterol in the coronary vessels of transplants to be ten times higher than those in comparable native coronary vessels of nontransplanted hearts. The lipid content of the arterial wall was found to correlate to a high degree with percentage stenosis of the coronary vessel lumen. Accumulation of lipids and cholesterol in the vessel wall appears to be an early, and the most important, predictor of development of GCV. In contrast, elevation of triglycerides alone has not been linked to the development of GCV.[37,41] Although some studies have associated the presence of pathologically elevated triglyceride levels in heart transplant recipients with an increased incidence of coronary stenosis as compared with patients with normal triglyceride levels, such an association has not been shown to be significant.[42] In a multicentre intravascular ultrasound study the combination of high triglyceride levels and low HDL cholesterol levels was found to correlate with increased intimal thickness.[43]

This presence of post-transplant hyperlipidaemia in the majority of patients early after heart transplantation emphasises the need for prophylactic lipid-lowering treatment immediately after transplantation.

3. Treatment of Hyperlipidaemia in Heart Transplant Recipients

In view of the aforementioned problems of hyperlipidaemia after heart transplantation (sections 1 and 2), treatment should be initiated as soon as possible postoperatively. The guidelines for treatment of hyperlipidaemia have evolved over the last 30 years on the basis of clinical information. The most recent recommendations of the National Cholesterol Education Program (NCEP) in the US were formulated by a panel of experts to optimise the benefits of treatment.[44] However, treatment of hyperlipidaemia after heart transplantation may require different guidelines. Hyperlipidaemia in these patients occurs early after transplantation. Potential treatment strategies include dietary measures, modification of immunosuppressive regimen and lipid-lowering drug therapy.

3.1 Dietary Measures

Systematic observance of a low cholesterol diet is the method of treating elevated LDL cholesterol levels in heart transplant recipients with the lowest incidence of adverse effects. All patients, together with their partners, should receive extensive dietary counselling. The aim should be observance of an American Heart Association (AHA) step I or step II diet.[45] More ambitious dietary measures, although useful and desirable, are not satisfactorily tolerated by patients in the long term. Dietary measures alone are not a sufficient means of treating hypercholesterolaemia in heart transplant recipients, since most patients show persistent elevation of lipid levels despite following their diet. In a study in which heart transplant recipients were followed up for 12 months postoperatively, a dietary programme failed to bring about any striking change in lipoprotein profile, both LDL cholesterol and triglycerides remaining elevated.[20] It was notable that despite good dietary observance, optimal drug treatment of hypertension and improved immunosuppressive therapy, the patients still showed elevated lipid levels. This indicates that drug therapy is required.

3.2 Modification of Immunosuppressive Therapy

Immunosuppressive agents, in particular ciclosporin and prednisolone, play a significant role in the development of post-transplant hyperlipidaemia.[20] One way of treating hyperlipidaemia is, therefore, to modify the patient's immunosuppressive regimen. This can involve one or both of these immunosuppressive agents. Many US transplant centres have attempted to reduce cholesterol levels in heart transplant recipients by dose reduction or discontinuation of corticosteroids;[46-48] however, the effectiveness of this measure has been highly variable. Reductions of between 6% and 26% in total cholesterol level have been achieved, but not

all patients benefited from this measure. Between 56% and 89% of the transplant recipients investigated showed reductions in lipid levels after discontinuation or dose reduction of corticosteroids.[47,48] However, the results of these studies indicate that elimination of corticosteroids from the immunosuppressive regimen does not necessarily lead to a reduction in cardiovascular risk profile. In another study, use of a steroid-free immunosuppressive regimen led to a 16% and 17% reduction in total and LDL cholesterol levels, respectively.[49] However, HDL cholesterol decreased at the same time by 18%, with the result that the patients' cardiovascular risk profile was not significantly improved.

Another approach is the use of new immunosuppressive agents. At present the best known new generation immunosuppressive agent is tacrolimus (FK-506). In a number of clinical trials, tacrolimus not only achieved significantly better results in terms of reduced graft rejection but also caused significantly less postoperative elevation of cholesterol levels, as compared with ciclosporin.[50] Total cholesterol was found to be 13% and LDL cholesterol 12% less than in patients treated with ciclosporin. These findings were later reproduced in renal and liver transplant recipients.[51,52] Another new immunosuppressive agent is sirolimus (rapamycin). Sirolimus did not significantly increase cholesterol levels compared with ciclosporin.[53-55] In randomised trials, the use sirolimus led to significantly reduced development of GCV compared with standard care (ciclosporin, prednisolone, azathioprine).[56,57]

Mycophenolate mofetil is another potent new immunosuppressive agent and it is available for oral administration. In experimental models it prolonged survival of allogeneic transplants. Inhibition of proliferative arteriopathy was observed in cardiac allografts. Elevation of total cholesterol was registered in 41% of studied patients.[58,59]

3.3 Drug Therapy

A variety of drugs belonging to a number of drug classes that differ in terms of their ability to favourably alter lipid levels, tolerability and adverse effects are available for the treatment of hypercholesterolaemia after heart transplantation. They include fibric acid derivatives, probucol, omega-3 fatty acids, bile acid binding agents, nicotinic acid derivatives, HMG-CoA reductase inhibitors (statins) and cholesterol absorption inhibitors (table I).

3.3.1 Fibric Acid Derivatives

The fibric acid derivatives most commonly used in antihyperlipidaemic therapy are gemfibrozil, clofibrate, bezafibrate and fenofibrate. These drugs are mostly used in patients with considerably elevated triglyceride levels. Reductions in levels of total cholesterol and its various fractions are generally only moderate, at 15–20%.[60] Therefore, use of fibric acid derivatives alone is only rarely indicated in heart transplant recipients, since hypercholesterolaemia is generally the most prominent lipid abnormality in this group. Only patients whose hypercholesterolaemia is accompanied by hypertriglyceridaemia are candidates for adjuvant therapy with fibric acid derivatives.[61] The gastrointestinal adverse effects of these drugs have been found to be an unfavourable factor for good patient compliance. Elevation of urea and creatinine levels, and reduction of renal function have often been observed during treatment with fibric acid derivatives, particularly in heart transplant recipients.[61] Intestinal absorption of ciclosporin is impaired during treatment with fibric acid derivatives, sometimes resulting in large fluctuations in blood ciclosporin concentrations.[62] Only in a small study group of heart transplant patients was gemfibrozil well tolerated and found not to interfere with immunosuppressive treatment.[20]

3.3.2 Probucol

Probucol has been used only rarely, namely in patients who are intolerant of other antihyperlipidaemic agents. Probucol lowers both total and LDL cholesterol levels by about 15%. It also delays oxidation of LDL cholesterol. A reduction of HDL cholesterol has also been observed. It has no effect on triglycerides.[63] In heart transplant recipients probucol has been found to be well tolerated but to reduce ciclosporin concentrations by up to 28%.[63]

Table I. Summary of antihyperlipidaemic drugs for use after heart transplantation

Drug class	Drug	Adverse effects	Risks
Fibric acid derivatives	Gemfibrozil Clofibrate Bezafibrate Fenofibrate	Renal dysfunction, nausea, gastrointestinal upset, gallstones, myositis, ciclosporin interaction	Increased risk of myositis in combination with statins, ciclosporin concentration disturbances, renal dysfunction
Antioxidants	Probucol	Decreased high-density lipoprotein, flatulence, loose stools, prolonged QT interval on ECG	Fluctuation of ciclosporin concentrations
Bile acid-binding agents	Colestyramine Colestipol	Constipation, bloating, malabsorption of fat-soluble vitamins	Poor compliance, inhibits absorption of ciclosporin, may increase triglycerides
Omega-3 fatty acids	Eicosapentaenoic acid Docosahexaenoic acid	Flatulence	No risks known to date
Vitamins	Nicotinic acid (niacin)	Pruritus, flush syndrome, liver dysfunction, peptic ulcer disease, uric acid levels increases	Adverse effects may be exacerbated with ciclosporin use
Statins	Lovastatin Simvastatin Pravastatin Fluvastatin Atorvastatin	Flatulence, increase of liver enzymes, abdominal pain, sleeplessness, myositis, increased creatinine kinase levels	Increased risk of myositis with high-dose statins, ciclosporin concentration disturbances, rhabdomyolysis
Cholesterol absorption inhibitor	Ezetimibe	Flatulence, increased liver enzymes, abdominal pain	Ciclosporin concentration disturbances

To date, probucol has had no therapeutic impact in transplant patients.

3.3.3 Omega-3 Fatty Acids

Epidemiological studies have shown an inverse correlation between consumption of fish or other sources of dietary omega-3 (n-3) fatty acids and cardiovascular events.[64] Numerous mechanisms of action have been described as accounting for the favourable effect of dietary n-3 fatty acids on factors implicated in the pathogenesis of atherosclerosis.[65]

Preliminary studies suggest that heart transplant recipients could be an interesting focus of investigation. Large doses of n-3 fatty acids lower cholesterol levels.[66] LDL cholesterol appears to increase dose dependently to some extent with n-3 supplementation, the apparent increase in LDL particle size, not the number of particles, being considered favourable. Increased HDL cholesterol levels in response to n-3 supplementation were observed in most, but not all, studies.[64] In heart transplant patients, endothelium-dependent coronary vasodilation, as assessed after acetylic infusion, was normal after 3 weeks of consuming 5g dietary n-3 fatty acids a day, whereas it was pathological in otherwise matched controls.[66] This could contribute to the inhibition of GCV and longer cardiac graft survival seen in animal models of cardiac transplantation.[67] Whether n-3 fatty acids influence heart transplant survival is currently under discussion.[68]

3.3.4 Bile Acid Binding Agents

Bile acid binding agents (or ion exchange resins) such as colestipol and colestyramine (cholestyramine), bind to bile acids inhibiting their reabsorption and, thereby, interrupting their enterohepatic circulation. This results in increased intrahepatic synthesis of bile acids and increased hepatic LDL receptor activity, leading to increased clearance of circulating LDL cholesterol. This mechanism of action suggests that intestinal absorption of lipid-soluble substances such as ciclosporin could be disturbed. In clinical trials in heart transplant recipients treatment with colestyramine led to a 14% reduction in total cholesterol level.[69] However, at the same time, unusually wide fluctuations in blood ciclosporin concentrations were observed. Moreover, bile acid-binding antihyperlipidaemic drugs were found to increase serum triglyceride levels in heart transplant recipients.[70] Because of these undesirable effects, bile acid-binding agents are of

only limited usefulness in heart transplant recipients.

3.3.5 HMG-CoA Reductase Inhibitors (Statins)

By inhibiting HMG-CoA reductase, the key enzyme of cholesterol biosynthesis, substances of the statin class (lovastatin, pravastatin, simvastatin, fluvastatin and atorvastatin) directly reduce the biosynthesis of cholesterol. This causes a marked reduction in cholesterol concentration in hepatocytes. This shortage of intracellular cholesterol leads to a compensatory increase in the number of newly formed LDL receptors in the liver. By increasing the uptake of LDL cholesterol, these newly formed LDL receptors bring about a marked reduction in the blood cholesterol levels.[71] Statins have been shown in a number of prospective, randomised, long-term studies to significantly reduce total and LDL cholesterol levels. They also achieved a significant increase in patient survival times and a significant reduction in the number of late coronary events.[6-8]

As in general medicine, the introduction of statins constituted a breakthrough in the treatment of hypercholesterolaemia in transplantation medicine. The first therapeutic trial of a statin in heart transplant recipients was conducted in 1988 using lovastatin.[72] Despite their good cholesterol-lowering properties, statins were at first used cautiously in heart transplant recipients because of the isolated occurrence of serious adverse effects. In particular, severe myopathy and even rhabdomyolysis were observed.[73] It must be noted that these events occurred in patients given doses of statins that are usual for patients who have not undergone a heart transplant (table II).[74]

Statins are metabolised in the liver via the cytochrome P450 (CYP) system. Simultaneous administration of the immunosuppressant ciclosporin, which is also metabolised via CYP, can lead to an increase in the plasma concentration of both drugs. Excessive plasma statin concentrations can cause myopathy and even rhabdomyolysis.[71,73] However, these risks can be largely eliminated by regular monitoring of liver enzymes (e.g. transaminases), bilirubin, and muscle enzyme levels (e.g. creatine kinase), and determining drug concentrations as well as adjusting dosages appropriately during the first months of statin therapy.

The primary objective of antihyperlipidaemic therapy is to reduce total and LDL cholesterol to levels at which the risk for atherosclerosis is low. In secondary prevention studies on nontransplanted coronary patients, treatment with simvastatin led to an approximately 33% reduction in mortality and an approximately 42% reduction in myocardial infarction risk.[7] On the basis of these excellent results, lovastatin, pravastatin and simvastatin were introduced into transplantation medicine. A number of authors reported 25–32% reductions in total cholesterol level within 6–96 months after transplantation, while LDL cholesterol was reduced by 40% from baseline levels.[20,72,75-85] These studies are summarised in table III. Although there have been many observational studies on the use of statins in heart transplant recipients, to date there have been only two prospective randomised studies on this subject; these investigated the long-term effects of pravastatin and simvastatin in heart transplant recipients.[81,85,86]

Table II. Case reports of creatine kinase elevation and rhabdomyolysis in heart transplant recipients receiving lovastatin

Author (year)	Lovastatin/ dosage	Combination with other drugs	No. of patients	Follow up (months)	Creatine kinase (U/L)
Corpier et al.[87] (1988)	80 mg/day		1	9	8.920
	80 mg/day		1	14	23.832
Norman et al.[88] (1988)	80 mg/day	Nicotinic acid	1	9	178.000 (rhabdomyolysis)
East et al.[73] (1988)	40 mg/day		1	1.5	29.920
	40 mg/dL		1	9	14.140
Ballantyne et al.[20] (1992)	40 mg/dL	Gemfibrozil	1	10	12.000
	80 mg/dL	Nicotinic acid	1	8	1.122

Table III. Studies on the use of HMG-CoA reductase inhibitors (statins) after heart transplantation

Author (year)	Drug	Dosage (mg/day)	No. of patients	Follow up (months)	Lipid change	Adverse effects
Kuo et al.[72] (1989)	Lovastatin	20–60	11	12	TC: −29% LDL-C: −32%	No adverse effects reported
Kobashigawa et al.[75] (1990)	Lovastatin	10–40	44	3	TC: −26% LDL-C: −25%	Rhabdomyolysis in one patient (40mg)
Ballantyne et al.[20] (1992)	Lovastatin	20	15	13	TC: −21% LDL-C: −31%	Muscle pain in one patient
Kobashigawa et al.[77] (1993)	Pravastatin	20–40	44	3	TC: −19% LDL-C: −18%	No adverse effects reported
Barbir et al.[76] (1991)	Simvastatin	10	12	8	TC: −38% LDL-C: −42%	No adverse effects reported
Vanhaecke et al.[78] (1994)	Simvastatin	5–20	25	6	TC: −27% LDL-C: −40%	No adverse effects reported
Carrier et al.[79] (1994)	Simvastatin	10	46	36	TC: −20% LDL-C: −36%	No adverse effects reported
Campana et al.[80] (1995)	Simvastatin	10	20	4	TC: −14% LDL-C: −21%	No adverse effects reported
Kobashigawa et al.[81] (1995)	Pravastatin	40	47	12	TC: −22% LDL-C: −27%	No adverse effects reported
Wenke et al.[82] (1995)	Simvastatin	5–20	33	24	TC: −29% LDL-C: −35%	No adverse effects reported
Pflugfelder et al.[83] (1995)	Simvastatin	10	13	12	TC: −32% LDL-C: −35%	No adverse effects reported
Mehra et al.[84] (2002)	Simvastatin	20	26	12	LDL-C: −23%	No adverse effects reported
Wenke et al.[85] (2003)	Simvastatin	5–20	35	96	TC: −27% LDL-C: −34%	No adverse effects reported

LDL-C = low-density lipoprotein cholesterol; **TC** = total cholesterol.

In the first of these studies, 97 heart transplant recipients were treated in the early postoperative period with either pravastatin 40 mg/day (n = 47) or diet alone (n = 50) as a control.[81] Total cholesterol levels over the first year were significantly lower in the active treatment group than in the control group, at 193 mg/dL (5 mmol/L) versus 248 mg/dL (6.4 mmol/L) [$p < 0.001$]. In addition to the cholesterol-lowering effect of pravastatin, other positive effects were observed. In particular, the incidence of clinically severe, haemodynamically relevant graft rejection in the first year was significantly less with pravastatin than in the control group. Also, the 1-year survival rate was significantly greater in the patients treated with pravastatin than in the control group, at 94% versus 78%, respectively ($p < 0.02$). The incidence of GCV as determined by angiography or autopsy was significantly lower in the pravastatin group and intracoronary ultrasound showed significantly less intimal thickening in the pravastatin group than in the control patients. Another positive effect of pravastatin therapy was a reduction in the cytotoxicity of natural killer cells. This effect of pravastatin was subsequently also observed in prospective randomised studies on renal transplant recipients.[81]

A second prospective, randomised study investigated simvastatin over a period of 8 years.[85] Thirty-five patients received simvastatin 5–20 mg/day, while 37 patients in a control group were treated with diet alone. At study end, the survival rate was significantly higher in the active treatment group than in the control group, at 88.6% versus 59.5% ($p < 0.006$), and the incidence of angiographically confirmed GCV was significantly lower in the active treatment than the control group, at 24.9% versus 54.7% ($p < 0.02$).[85] After 4 study years the intimal thickness of the coronary vessels as determined by intracoronary ultrasound in a subgroup of 27 patients was significantly less in the active treat-

ment group than in the control group ($p < 0.045$). Reduced rejection activity was evidenced by a tendency toward less severe rejection reactions and associated graft failure in the active treatment group than in the control group.[86] Nevertheless, the total number of graft rejections confirmed by biopsy did not differ significantly between the two groups.[85,86]

In both studies the statin used (pravastatin and simvastatin, respectively) was well tolerated. No severe adverse effects were observed. There were isolated elevations of creatine kinase; however, all of these proved reversible and none was accompanied by myolysis. No cases of rhabdomyolysis were reported in either study, nor were there any reports of interactions between either statin and any component of the patients' immunosuppressive therapy, in particular ciclosporin. In the interests of drug safety, hepatic and renal function were closely monitored in both studies. The statins were given at low dosages throughout the study in order to avoid accumulation and resulting abnormal serum levels of the substances.

In both studies the positive effects of statin therapy were not limited to cholesterol reduction. Of course, systematic and effective cholesterol reduction is of central importance since, as demonstrated in a number of large-scale randomised intervention studies in the general patient population,[6-8] it results in less progression of coronary heart disease, significantly fewer cardiac events and significantly better survival rates. These effects can also be demonstrated in heart transplant recipients. However, in addition to cholesterol reduction, statins appear to exert other actions that play a crucial role in the pathogenesis of GCV. For example, simvastatin is known to inhibit proliferation of VSMC, an important process in the pathogenesis of atherosclerotic lesions.[89] In addition, statins exert a direct influence on the gene expression of growth factors that are required for proliferation of VSMC.[90] Furthermore, simvastatin has been found to exert a direct influence on the gene expression of endothelin-1 in cultured endothelial cells, thereby markedly improving endothelial function and consequently providing protection against atherosclerosis.[91] Monocyte adhesion to endothelial cells, a crucial step in the formation of atherosclerotic plaques, is similarly inhibited by simvastatin.[92] Statins also significantly improve epicardial and microvascular endothelial function in heart transplant patients: after a year of statin therapy coronary endothelial function and cardiac cytokine activity were found to be significantly better than in untreated patients.[93]Acting synergistically, these various effects can considerably reduce the incidence of GCV in patients receiving systematic statin therapy.

Statins may also have immunomodulatory effects. In both the transplantation studies described here the survival rate was significantly better in the patients treated with statins. This was mostly due to a lower rate of severe rejection reactions and associated graft failure. This phenomenon is interesting insofar as statins themselves have no immunosuppressive actions;[94] however, in the presence of the immunosuppressant ciclosporin, statins appear to develop such actions. Thus, they have been reported to reduce the number of natural killer cells, inhibit T-cell proliferation and reduce T-cell cytotoxicity, suppress T-cell responses, reduce chemokine synthesis in peripheral blood mononuclear cells and inhibit expression of MHC-II genes.[95-100] In order to explain these effects of statins, it might be postulated that statin-induced LDL receptor activation also results in increased intracellular availability of LDL-bound ciclosporin and, thus, more inhibition of immunologically competent cells.

3.3.6 Cholesterol Absorption Inhibitors

A completely new class of cholesterol-lowering drugs, namely selective cholesterol absorption inhibitors, has now become available. So far, ezetimibe is the only available representative of this group.[101]

In nontransplant recipients, ezetimibe significantly reduces total and LDL cholesterol, apolipoprotein B and triglyceride levels while increasing HDL cholesterol levels. These effects are due to selective inhibition of intestinal absorption of cholesterol and related phytosterols, and are seen both with monotherapy and when the drug is used in combination with statins.[102] Treatment with eze-

timibe should be initiated with caution in patients receiving ciclosporin, since increased plasma ezetimibe concentrations have been reported in combination with ciclosporin. In particular, many immunosuppressive agents are metabolised via the CYP system and competition between substances for this system can cause drug interactions.[101-104]

To date, little clinical experience is available on the use of ezetimibe in heart transplant patients.

3.4 Heparin-Induced Extracorporeal Low-Density Lipoprotein Precipitation (HELP)

In a small proportion of heart transplant recipients with heterozygous familial hypercholesterolaemia, even maximal dietary and drug therapy fails to reduce LDL cholesterol to target levels of <100 mg/dL (2.6 mmol/L).[105] In this group of patients drug therapy can be supplemented by extracorporeal treatment methods that can reduce the elevated LDL cholesterol levels to within the target range. As well as bringing about a maximal reduction in LDL cholesterol level, the heparin-induced extracorporeal LDL precipitation (HELP) system has significant haemorheological benefits resulting from reduction of fibrinogen and Lp(a) levels.[106] The HELP system is based on precipitation of LDL cholesterol from the plasma. This is induced by heparinisation and acidification of the plasma (pH 5.12). The precipitated LDL cholesterol is eliminated by means of an extracorporeal filter system and the purified plasma is then returned to the patient's blood circulation (figure 1). The procedure takes about 150–180 minutes.

The HELP system was first used in heart transplant recipients with familial hypercholesterolaemia in 1991.[107,108] In the small group of patients studied, the mean LDL cholesterol level of 172 mg/dL (4.45 mmol/L) achieved with the aid of diet and statins was reduced to 125 mg/dL (3.2 mmol/L) by means of the HELP system. The procedure had no influence on the blood ciclosporin levels, nor were any other negative effects observed. The heart transplant recipients treated in this way showed no increased incidence of infections and no impairment of organ function attributable to the procedure.[107,108] Other authors have reported achieving significant regression of existing GCV with the aid of the HELP system.[109,110]

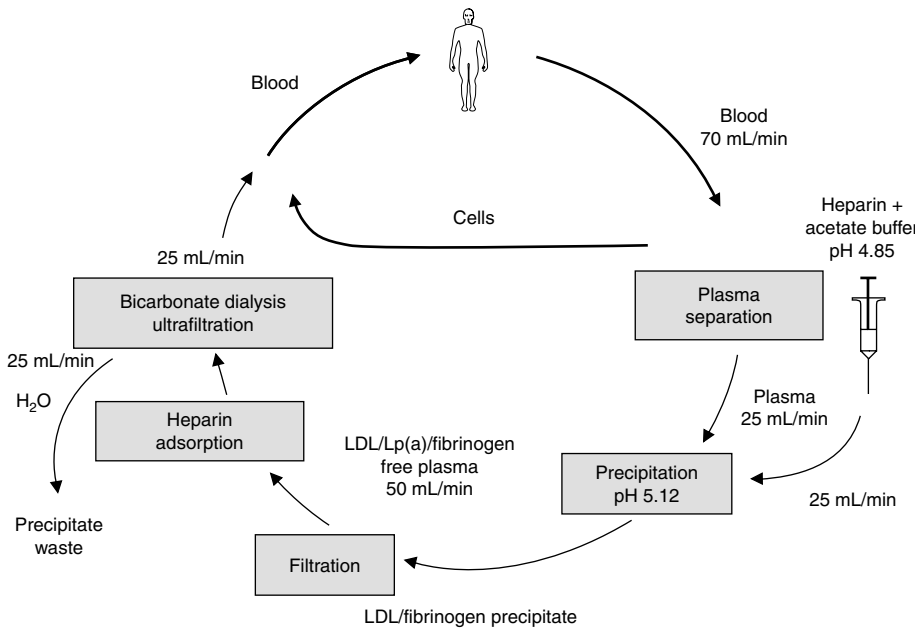

Fig. 1. Flow chart of heparin induced extracorporeal low-density lipoprotein (LDL) precipitation (HELP). **Lp(a)** = lipoprotein (a).

In a controlled trial in 20 heart transplant patients with severe hypercholesterolaemia, regular weekly use of the HELP technique in combination with simvastatin (n = 10) led to a significant reduction in fibrinogen, LDL cholesterol and Lp(a) levels, and a lower incidence of GCV compared with patients treated with simvastatin alone. However, the criteria for assessment of newly diagnosed GCV were not clearly defined in this study.[111]

The HELP system is costly, time consuming and of potential benefit only to a small proportion of heart transplant recipients; it is, therefore, available only in a small number of major treatment centres.

4. Summary and Recommendations

More than 60% of heart transplant recipients develop elevated lipids levels, especially LDL cholesterol, postoperatively. Dietary factors, genetic predisposition and immunosuppressive agents have been identified as the principal causes of hypercholesterolaemia in transplant recipients. Elevated cholesterol levels correlate in heart transplant recipients with an increased risk for GCV and other vascular disorders. Although urgently needed, internationally accepted guidelines for drug therapy in heart transplant recipients are still lacking.

Guidelines for the treatment of hyperlipidaemia in heart transplant recipients should be based on the NCEP guidelines (figure 2). According to these, lipid-lowering therapy should be initiated in all patients with a total cholesterol >200 mg/dL (5.2 mmol/L), LDL cholesterol >130 mg/dL (3.4 mmol/L) and triglycerides >200 mg/dL (2.26 mmol/L), while LDL cholesterol >100 mg/dL (2.6 mmol/L) and triglycerides >150 mg/dL (1.7 mmol/L) constitute relative indications. Lipid-lowering therapy should be initiated considerably earlier and be more aggressive in heart transplant patients than in non-transplant patients, as GCV develops soon after transplantation and can become clinically relevant within a year.

The statins are the most intensively investigated of the drugs currently available for lowering cholesterol levels in heart transplant recipients. In addition to their cholesterol-lowering effect, these drugs have

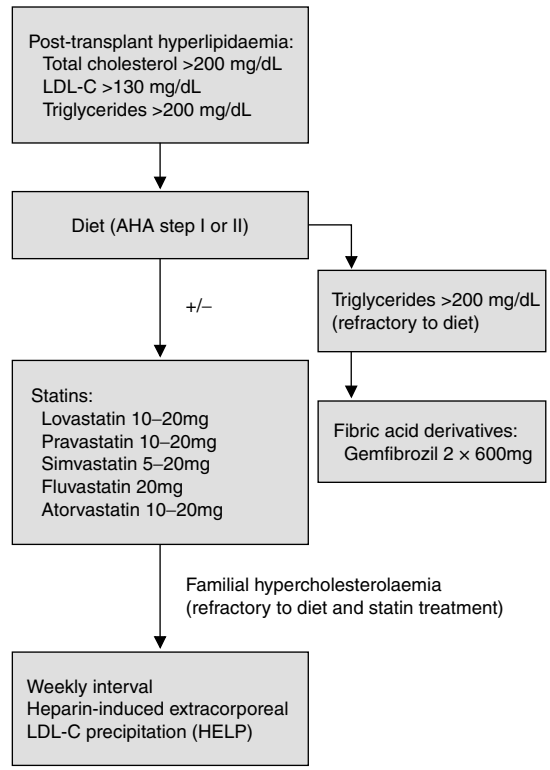

Fig. 2. Treatment algorithm for hyperlipidaemia in heart transplant recipients. **AHA** = American Heart Association; **HELP** = heparin-induced extracorporeal LDL precipitation; **LDL-C** = low-density lipoprotein-cholesterol.

demonstrated immunomodulatory effects both *in vitro* and *in vivo*. Their clinical use has resulted in significantly better survival rates, a significantly lower incidence of GCV and fewer severe graft rejections. Statin therapy in combination with a systematic diet (AHA step I or II) should, therefore, be initiated in all heart transplant recipients as soon as possible after transplantation. Any of the currently available statins – lovastatin, pravastatin, simvastatin, fluvastatin or atorvastatin – can be used. The organ-specific dosage guidelines for these substances must be rigidly adhered to, and careful biochemical and clinical monitoring of patients in order to minimise the risk of myositis and rhabdomyolysis is required.

Treatment with fibric acid derivatives (e.g. gemfibrozil) may be considered in heart transplant

patients with hypertriglyceridaemia (>150–200 mg/dL; >1.7–2.26 mmol/L) that cannot be controlled by diet alone. However, strict observance of safety instructions and regular monitoring of renal function are required.

Extracorporeal cholesterol elimination procedures, such as HELP, are required in only a small number of patients with familial hypercholesterolaemia refractory to diet and cholesterol-lowering drug treatment, but when required they can be performed in heart transplant recipients without risk or complication. Currently used forms of treatment may in the future be supplemented or replaced by selective cholesterol absorption inhibitors.

Acknowledgements

The author has provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

References

1. Miller LW, Schlant RC, Kobashigawa JA, et al. 24th Bethesda Conference: cardiac transplantation. Task force 5: complications. J Am Coll Cardiol 1993; 22: 41-54
2. Grady KL, Costanzo-Nordin MR, Herold LS, et al. Obesity and hyperlipidemia after heart transplantation. J Heart Lung Transplant 1991; 10: 449-54
3. Taylor DO, Thompson JA, Hastillo A, et al. Hyperlipidemia after clinical heart transplantation. J Heart Transplant 1989; 8: 209-13
4. Chan MK, Varghese Z, Moorhead JF. Lipid abnormalities in uremia, dialysis and transplantation. Kidney Int 1981; 19: 625-37
5. Ibels LS, Simons LA, King JO, et al. Studies on the nature and causes of hyperlipidemia in uraemia, maintenance dialysis and renal transplantation. Q J Med 1975; 44: 601-14
6. Shepard J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333: 1301-7
7. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary artery disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-9
8. Heart Protection Collaborative Group. MRC/BHF heart protection study of cholesterol with simvastatin in 20536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360: 7-22
9. Miller LW. Allograft vascular disease: a disease not limited to hearts. J Heart Lung Transplant 1992; 11 (3 Pt 2): S32-7
10. Gao SZ, Schroeder JS, Alderman EL, et al. Clinical and laboratory correlates of accelerated coronary artery disease in cardiac transplant patients. Circulation 1987; 76: 56-61
11. McGriffin DC, Savumen T, Kirklin JK, et al. Cardiac transplant coronary disease: a multivariate analysis of pretransplant risk factors for disease development and morbid events. J Thorac Cardiovasc Surg 1995; 109: 1081-9
12. PerraultL P, Mahlberg F, Breugnot C, et al. Hypercholesterolemia increases coronary endothelial dysfunction, lipid content, and accelerated atherosclerosis after heart transplantation. Arterioscler Thromb Vasc Biol 2000; 20: 728-36
13. Shi C, Lee WS, Russell ME, et al. Hypercholesterolemia exacerbates transplant arteriosclerosis via increased neointimal smooth muscle cell accumulation: studies in apolipoprotein E knockout mice. Circulation 1997; 96: 2722-8
14. Esper E, Glagov S, KIarp RB, et al. Role of hypercholesterolemia in accelerated transplant coronary vasculopathy: results of surgical therapy with partial ideal bypass in rabbits undergoing heterotopic heart transplantation. J Heart Lung Transplant 1997; 16: 420-35
15. Scheidt VW, Kemkes BM, Reichart B, et al. Percutaneous transluminal coronary angioplasty of focal coronary lesions after heart transplantation. Clin Invest 1993; 71: 524-30
16. Bull DA, Hunter GC, Copeland JG, et al. Peripheral vascular disease in heart transplant recipients. J Vasc Surg 1992; 16: 546-53
17. Carrier M, Rivard M, Kostuk W, et al. The Canadian study of cardiac transplantation atherosclerosis. Can J Cardiol 1999; 15: 1337-44
18. Farmer JA, Ballantyne CM, Frazier OH, et al. Lipoprotein(a) and apolipoprotein changes after cardiac transplantation. J Am Coll Cardiol 1991; 18: 926-30
19. Gao SZ, Schroeder JA, Alderman EL, et al. Prevalence of accelerated coronary artery disease in heart transplant survivors: comparison of cyclosporine and azathioprine regimens. Circulation 1989; 80 Suppl. 3: III-100
20. Ballantyne CM, Radovancevic B, Farmer JA, et al. Hyperlipidemia after heart transplantation: report of a 6-year experience with treatment recommendations. J Am Coll Cardiol 1992; 19: 1315-21
21. Hosenpud JD, Shipley GD, Wagner CR. Cardiac allograft vasculopathy: current concepts, recent developments, and future directions. J Heart Lung Transplant 1992; 11: 9-23
22. Barbir M, Kushwaha S, Hunt B, et al. Lipoprotein (a) and accelerated coronary artery disease in cardiac transplant recipients. Lancet 1992; 340: 1500-2
23. Kobashigawa JA, Kasiske BL. Hyperlipidemia in solid organ transplantation. Transplantation 1997; 63: 331-8
24. Becker DM, Chamberlain B, Swank R, et al. Relationship between corticosteroid exposure and plasma lipid levels in heart transplant recipients. Am J Med 1988; 85: 632-8
25. Augustine SM, Baumgartner WA, Kasper EK. Obesity and hypercholesterolemia following heart transplantation. J Transpl Coord 1998; 8: 164-9
26. De Groen PC. Cyclosporine, low density lipoprotein, and cholesterol. Mayo Clin Proc 1988; 63: 1012-21
27. Kemna MS, Valentine HA, Hunt SA, et al. Metabolic risk factors for atheroslcerosis in heart transplant recipients. Am Heart J 1994; 128: 68-72
28. Bagdade JD, Lane JT, Subbaiah PV, et al. Accelerated cholesteryl ester transfer in non-insulin dependent diabetes mellitus. Atherosclerosis 1993; 104: 69-78
29. Valantine HA, Schroeder JS. HMG-CoA reductase inhibitors reduce transplant coronary artery disease and mortality. Circulation 1997; 96: 1370-3
30. Johnson DE, Aldermann EL, Schroeder JS, et al. Transplant coronary artery disease: histopathological correlations with

angiographic morphology. J Am Coll Cardiol 1991; 17: 449-57
31. St Goar FG, Pinto FJ, Aldermann EL, et al. Intracoronary ultrasound in cardiac transplant recipients: *in vivo* evidence of angiographically silent intimal thickening. Circulation 1992; 85: 979-87
32. Rickenbacher PR, Pinto FJ, Lewis NP, et al. Prognostic importance of intimal thickness as measured by intracoronary ultrasound after cardiac transplantation. Circulation 1995; 93: 3445-52
33. Gao SZ, Alderman EL, Schroeder JS, et al. Progressive coronary luminal narrowing after cardiac transplantation. Circulation 1990; 82: 269-75
34. Barbir M, Banner N, Thompson GR, et al. Relationship of immunosuppression and serum lipids to the development of coronary arterial disease in the transplanted heart. Int J Cardiol 1991; 32: 51-6
35. Bieber CP, Hunt SA, Schwinn DA, et al. Complications in long-term survivors of cardiac transplantation. Transplant Proc 1981; 13 (1): 207-11
36. Paavonen T, Mennander A, Lautenschlager I, et al. Endothelialitis and accelerated arteriosclerosis in human heart transplant coronaries. J Heart Lung Transplant 1993; 12: 117-22
37. McManus BM, Horley KJ, Wilson JE, et al. Prominence of coronary arterial wall lipids in human heart allografts: implications for pathogenesis of allograft arteriopathy. Am J Pathol 1995; 147: 293-308
38. Libby P, Swanson SJ, Tanaka H, et al. Immunopathology of coronary arteriosclerosis in transplanted hearts. J Heart Lung Transplant 1992; 11: 5-6
39. Ross R. The pathogenesis of atherosclerosis: an update. N Engl J Med 1986; 314: 488-500
40. Allen MD, McDonald TO, Carlos T. Endothelial adhesion molecules in heart transplantation. J Heart Lung Transplant 1992; 11: 8-13
41. Cooper A, Heagerty AM. Endothelial dysfunction in human intramyocardial small arteries in atherosclerosis and hypercholesterolemia. Am J Physiol 1998; 275: 1482-8
42. Winters GL, Kendall TJ, Radio SJ, et al. Posttransplant obesity and hyperlipidemia: major predictors of severity of coronary arteriopathy in failed human heart allografts. J Heart Transplant 1990; 9 (4): 364-71
43. Valantine HA. Role of lipids in allograft vascular disease: a multicenter study of intimal thickening detected by intravascular ultrasound. J Heart Lung Transplant 1995; 14: 234-7
44. The Expert Panel III. National Cholesterol Education Program. JAMA 2001; 285: 2486-95
45. Adult Treatment Panel II. Summery of the second report of the National Cholesterol Education Program. JAMA 1993; 269: 3015-23
46. Renlund DG, Bristow MR, Crandall BG, et al. Hypercholesterolemia after heart transplantation: amerlioration by corticosteroid-free maintenance immunosuppression. J Heart Lung Transplant 1989; 8: 214-9
47. Keogh A, Macdonald P, Harvison A, et al. Initial steroid-free versus steroid-based maintenance therapy and steroid withdrawal after heart transplantation: two views of the steroid question. J Heart Lung Transplant 1992; 11: 421-7
48. Kobashigawa JA, Stevenson LW, Brownfield EB, et al. Corticosteroid weaning late after cardiac transplantation: relation to HLA-DR mismatching and long-term metabolic benefits. J Heart Lung Transplant 1995; 14: 963-7
49. Hricik DE, Bartucci MR, Mayes JT. The effects of steroid withdrawal on the lipoprotein profiles of cyclosporine-treated kidney and kidney-pancreas transplant recipients. Transplantation 1992; 54: 868-71
50. Taylor DO, Barr ML, Radovancevic B, et al. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant 1999; 18: 336-45
51. McCune TR, Thacker LR, Peters TG, et al. Effects of tacrolimus on hyperlipidemia after successful renal transplantation. Transplantation 1998; 65: 87-92
52. Cleasson K, Mayer AD, Squifflet JP, et al. Lipoprotein patterns in renal transplant patients: a comparison between FK 506 and cyclosporine A patients. Tranplant Proc 1998; 30: 1292-4
53. Groth C, Backmann L, Morales J, et al. Sirolimus (rapamycin) based therapy in human renal transplantation. Transplantation 1999; 67: 1036-42
54. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomized multicenter study. Lancet 2000; 356: 194-202
55. Edelman ER, Danenberg HD. Rapamycin for cardiac transplantrejection and vasculopathy: one stone, two birds. Circulation 2003; 108: 6-8
56. Mancini D, Pinney S, Burkhoff D, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation, 2003; 108: 48-53
57. Dambrin C, Klupp J, Birsan T, et al. Sirolimus monotherapy prevents graft vascular disease in non human primate recipients of orthotopic aortic allografts. Circulation 2003; 107: 2369-74
58. Gregory CR, Huang X, Pratt RE, et al. Treatment with rapamycin and mycophenolic acid reduces arterial intimal thickening produced by mechanical injury and allows endothelial replacement. Transplantation 1995; 59: 655-61
59. Bullingham RES, Nicholls A, Hale M. Pharmacokinetics of mycophenolate mofetil: a short review. Transplant Proc 1996; 28: 925-9
60. Biossonnat P, Salen P, Guidollet J, et al. The long-term effects of the lipid-lowering agent fenofibrate in hyperlipidemic heart transplant recipients. Transplantation 1994; 58: 245-7
61. Hidalgo L, Zambrana JL, Blanco-Molina A, et al. Lovastatin versus bezafibrate for hyperlipidemia treatment after heart transplantation. J Heart Lung Transplant 1995; 14: 461-7
62. Keogh A, Day R, Critchley L, et al. The effect of food and cholestyramine on the absorption of cyclosporine in cardiac transplant recipients. Transplant Proc 1988; 20 (1): 27-30
63. Sundararajan V, Cooper DKC, Muchmore J, et al. Interaction of cyclosporine and probucol in heart transplant patients. Transplant Proc 1991; 23: 2028-32
64. von Schacky C. n-3 fatty acids and the prevention of coronary atherosclerosis. Am J Clin Nutr 2000; 71: 224S-7S
65. Sarris GE, Mitchell RS, Billingham ME, et al. Inhibition of accelerated cardiac arteriosclerosis by fish oil. J Thorac Cardiovasc Surg 1989; 97: 841-55
66. Mozattarian D, Lemaitre RN, Kuller LH, et al. Cardiac benefits of fish oil consumption may depend on the type of fish meal consumed. Circulation 2003; 107: 1372-7
67. Grimminger F, Grimm H, Fuhrer D, et al. Omega-3 lipid infusion in a heart allotransplant model: shift in fatty acid and lipid mediator profiles and prolongation of transplant survival. Ciruculation 1996; 93: 365-71

68. Fleischhauer FJ, Yau WD, Fischell TA. Fish oil improves endothelium-dependent coronary vasodilatation in heart transplant recipients. J Am Coll Cardiol 1993; 343: 1454-9
69. Keogh A, Day R, Critchley L, et al. The effect of food and cholestyramine on the absorption of cyclosporine in cardiac transplant recipients. Transplant Proc 1988; 20: 27-30
70. Jensen RA, Lal SM, Diaz-Arias A, et al. Does cholestyramine interfere with cyclosporine absorption?: a prospective study in renal transplant patients. ASAIO J 1995; 41: 704-6
71. Plosker GL, McTavish D. Simvastatin: a reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolemia. Drugs 1995; 50: 334-63
72. Kuo PC, Kirshenbaum JM, Gordon J, et al. Lovastatin therapy for hypercholesterolemia in cardiac transplant recipients. Am J Cardiol 1989; 64: 631-5
73. East C, Alivizatos PA, Grundy SM, et al. Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation. N Engl J Med 1988; 318: 47-8
74. Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high risk patients. Arch Intern Med 2003; 163: 553-64
75. Kobashigawa JA, Murphy FL, Stevenson LW, et al. Low-dose lovastatin safely lowers cholesterol after cardiac transplantation. Circulation 1990; 82 (5 Suppl.): 281-3
76. Barbir M, Rose M, Kushwaha S, et al. Low-dose simvastatin for treatment of hypercholesterolemia in recipients of cardiac transplantation. Int J Cardiol 1991; 33: 241-6
77. Kobashigawa JA, Brownfield ED, Stevenson LW, et al. Effects of pravastatin for hypercholesterolemia in cardiac transplant recipients [abstract]. J Am Coll Cardiol 1993; 21: 141
78. Vanhaecke J, van Cleemput J, van Lierde J, et al. Safety and efficacy of low dose simvastatin in cardiac transplant recipients treated with cyclosporine. Transplantation 1994; 58: 42-5
79. Carrier M, Pelletier GB, Genest Jr J, et al. Cholesterol lowering intervention and coronary artery disease after cardiac transplantation. Ann Thorac Surg 1994; 57: 353-6
80. Campana C, Iacona I, Regazzi MB, et al. Efficacy and pharmacokinetics of simvastatin in heart transplant recipients. Ann Pharmacother 1995; 29: 235-9
81. Kobashigawa JA, Katznelson W, Laks H, et al. Effects of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995; 333: 621-7
82. Wenke K, Thiery J, Meiser B, et al. Long-term Simvastatin therapy for hypercholesterolemia in heart transplant recipients. Z Kardiol 1995; 84: 130-6
83. Pflugfelder PW, Huff M, Oskalns R, et al. Cholesterol-lowering therapy after heart transplantation: a 12-month randomized trial. J Heart Lung Tranplant 1995; 14: 613-22
84. Mehra MR, Uber PA, Vivekananthan K, et al. Comparative beneficial effects of simvastatin and pravastatin on cardiac allograft rejection and survival. J Am Coll Cardiol 2002; 40: 1609-14
85. Wenke K, Meiser B, Thiery J, et al. Simvastatin initiated early after heart transplantation: 8-year prospective experience. Circulation 2003; 107: 93-7
86. Wenke K, Meiser B, Thiery J, et al. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four year randomized trail. Circulation 1997; 96: 1398-402
87. Corpier CL, Jones PH, Suki WN, et al. Rhabdomyolysis and renal injury with lovastatin use: report of two cases in cardiac transplant recipients. JAMA 1988; 260: 239-41
88. Norman DJ, Illingworth DR, Munson J, et al. Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. N Engl J Med 1988; 318: 46-7
89. Corsini A, Raiteri M, Soma MR, et al. Simvastatin but not pravastatin has a direct inhibitory effect on rat and human myocyte proliferation. Clin Biochem 1992; 25: 399-400
90. Farmer JA. Pleiotropic effects of statins. Curr Atheroscler Rep 2000; 2: 208-17
91. Alfon J, Guasch JF, Berropze M, et al. Nitric oxide synthetase-II (NOS-II) gene expression correlates with atherosclerotic intimal thickening: preventive effects of HMG-CoA-reductase inhibitors. Atherosclerosis 1999; 145: 325-31
92. Hernandez-Perera O, Perea-Salea D, Navarro-Antolin J, et al. Effects of the 3-hydroxy-3-methylglutaryl-CoA-reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin I and endothelial nitric oxide synthetase in vascular endothelial cells. J Clin Invest 1998; 101: 2711-9
93. Weis M, Pehlivanli S, Meiser BM, et al. Simvastatin treatment is associated with improvement in coronary endothelial function and decreased cytokine activation in patients after heart transplantation. J Am Coll Cardiol 2001; 38: 814-8
94. Teupser D, Bruegel M, Stein O, et al. HMG-CoA reductase inhibitors reduce adhesion of human monocytes to endothelial cells. Biochem Biophys Res Commun 2001; 289: 838-44
95. Muldoon MF, Flory JD, Marsland A, et al. Effects of lovastatin on the immune system. Am J Cardiol 1997; 80: 1391-4
96. Katznelson S, Huang XM, Chia D, et al. The inhibitor effects of pravastatin on natural killer T-cell activity *in vivo* in cytotoxic T-lymphocyte activity *in vitro*. J Heart Lung Transplant 1998; 259: 414-9
97. McPherson R, Tsoukas C, Baines MG, et al. Effects of lovastatin on natural killer cell function and other immunological parameters in men. J Clin Immunol 1993; 13: 439-44
98. Kurakata S, Kada M, Shimada Y, et al. Effect of different inhibitors of 3-hydroxy 3-methylglutaryl- coenzyme A reductase, pravastatin sodium and simvastatin, on sterol synthesis and immunological functions in human lymphocyte *in vitro*. Immunopharmocol 1996; 34: 51-61
99. Kano H, Hayashi T, Sumi D, et al. A HMG-CoA reductase inhibitor improved progression of atherosclerosis in the rabbit aorta without affecting serum lipid levels: possible relevance of upregulation of endothelial nitric oxide synthetase mRNA. Biochem Biophys Res Commun 1999; 259: 414-9
100. Kwak B, Mulhaupt F, Myit S, et al. Statins as a newly recognized type of immunomodulator. Nat Med 2000; 80: 1095-100
101. Ballantyne CM. Ezetimibe: efficacy and safety in clinical trails. Eur Heart J Suppl 2002; 4 Suppl. J: 9-18
102. Gagné C, Gaudet D, Bruckert E, et al. Efficacy and safety of ezetimibe coadministered with atorvaststin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002; 105: 101-7
103. Stein E. Results of phase I/II clinical trials with ezetimibe, a novel selective cholesterol absorption inhibitor. Eur Heart J Suppl 2001; 3 Suppl. E: E11-6
104. Bays HE, Moore PB, Drehobl MA, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. Clin Ther 2001; 23: 1209-30
105. Thiery J, Meiser B, Wenke K, et al. Heparin-Induced Extracorporeal Low-Density-Lipoprotien Plasmapheresis (H.E.L.P.) and its use in heart transplant patients with severe hypercholesterolemia. Transplant Proc 1995; 27: 1950-3

106. Thiery J, Seidel D. LDL-apheresis: clinical experience and indications in the treatment of severe hypercholestererolemia. Transfus Sci 1993; 14: 249-59
107. Wenke K, Thiery J, Arndtz N, et al. Optimized and safe treatment of hypercholesterolemia after heart transplantation by low dose simvastatin and H.E.L.P.-apheresis [abstract]. Thorac Cardiovasc Surg 1992; 40: 124
108. Wenke K, Thiery J, Arndtz N, et al. Treatment of hypercholesterolemia and prevention of coronary artery disease after heart transplantation by combination of low-dose simvastatin and HELP-LDL-apheresis. Transplant Proc 1992; 24: 2674-6
109. Park JW, Vermeltfoort M, Braun P, et al. Regression of transplant coronary artery disease during chronic HELP therapy: a case study. Atherosclerosis 1995; 115: 1-8
110. Park J-W. Regression of transplant coronary artery disease during chronic H.E.L.P.-apheresis: a case report. In: Seidel D, editor. H.E.L.P. report 1994. Germany: MMV Verlag München, 1994: 27
111. Jaeger BR, Meiser B, Nagel D, et al. Aggressive lowering of fibrinogen and cholesterol in the prevention of graft vessel disease after heart transplantation. Circulation 1997; 96 Suppl. II: II-154-8

Correspondence and offprints: Dr *Klaus Wenke*, Division of Cardiac Surgery, Hospital Munich-Bogenhausen, Munich D-81925, Germany.
E-mail: klaus.wenke@extern.lrz-muenchen.de