Minireview

Dyslipidemia and Its Therapeutic Challenges in Renal Transplantation

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Cardiovascular disease is the leading cause of mortality in kidney transplant recipients. Dyslipidemia is a common finding after renal transplantation and a significant risk factor in the development of coronary heart disease. Although a causal relationship with cardiovascular mortality has not been proven in the transplant population, it is reasonable to extrapolate data from the general population and aggressively treat posttransplant dyslipidemia. Statins are considered the agents of choice, though their use may be complicated by drug misadventures. Pravastatin, fluvastatin and pitavastatin are considered to be the safest statins to use in this population; however, given their low-potency, a high-potency statin, such as atorvastatin, may be necessary in patients with significant dyslipidemia. In this article, we discuss the etiology of and treatment strategies for dyslipidemia in renal transplant recipients based on a literature review of potential therapeutic adverse effects and benefits in this population. We will also evaluate the reasons for and consequences of the latest Food and Drug Administration (FDA) warnings regarding the use of simvastatin.

Introduction

Cardiovascular disease is the leading cause of mortality after organ transplantation, accounting for more than 30% of deaths (1). With the improvement in short-term allograft survival in the past decade, death with a functioning allograft has become one of the major causes of graft loss (2). Consequently, reducing cardiovascular mortality is a major goal in posttransplant medical care. In addition to traditional cardiac risk factors, the pathogenesis of cardiovascular disease after transplantation involves transplant-specific factors, such as the duration of pretransplant end-stage renal disease, new onset posttransplant diabetes and poor allograft function (3).

Dyslipidemia is a frequent finding following transplantation and immunosuppressive medications play a central role in its pathogenesis. Historically, the prevalence of hyperlipidemia in renal transplant recipients (RTR) has been reported to be higher than 80% (4); however, recent data reflecting the use of more modern immunosuppressive regimens report that approximately 44% of RTR have a low-density lipoprotein (LDL) level above 100 mg/dL six months following transplantation (1,5), and that roughly 40% of RTR are treated with a 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitor (i.e. statin) (1,5).

In the general population, the correlation between elevated serum cholesterol and increased risk of coronary heart disease (CHD) is well established and reductions in serum LDL have proved to significantly reduce both morbidity and mortality of patients with or without CHD (6). Conversely, the role of dyslipidemia in posttransplant cardiovascular disease is not as clearly defined, though some literature suggests that assessment and treatment of dyslipidemia could decrease cardiovascular events posttransplantation (7). One recently recognized interesting aspect is that cardiovascular interventions may affect different cardiovascular outcomes, particularly as not all cardiac deaths are associated with atherosclerotic CHD. Therefore, while statins are beneficial in preventing cholesterol-dependent events (8,9), complementary interventions such as tight blood pressure control and preservation of renal function might be required for the prevention of cardiac deaths not

directly related to atherosclerosis (9), such as lethal arrhythmias.

In this review, we will discuss the etiologies of and treatment strategies for dyslipidemia in RTRs and evaluate the reasons and consequences of the latest Food and Drug Administration (FDA) warnings regarding the use of simvastatin.

Etiologies of Dyslipidemia in Transplantation

Potential causes of dyslipidemia posttransplantation include immunosuppressive medications, diet, obesity and genetic predisposition. Among the immunosuppressive agents, corticosteroids, cyclosporine and the mammalian target of rapamycin (mTOR) inhibitors are especially associated with elevations in lipid levels. The intensity of immunosuppressive therapy also seems to play an important role.

Corticosteroids have multiple potential deleterious effects on cholesterol metabolism, including an increase in the activity of acetyl-coenzyme A carboxylase and free fatty acid synthetase, down regulation of LDL receptor activity, increase in the activity of HMG-CoA reductase and inhibition of lipoprotein lipase (10). A high cumulative dose of corticosteroids is associated with increased levels of very low-density lipoproteins (VLDL), total cholesterol (TC), and triglycerides (TG), as well as a decrease in high-density lipoprotein (HDL) levels. This has been confirmed in early corticosteroid withdrawal analyses that show beneficial effects in reducing dyslipidemia (11).

Cyclosporine inhibits the enzyme 26-hydroxylase, which is important in the bile acid synthetic pathway, leading to a decrease in the synthesis of bile acids from cholesterol and its transport to the intestines (12). Among the calcineurin inhibitors, the Symphony trial reported a higher incidence of new onset dyslipidemia in patients on cyclosporine (36%) compared to those treated with low-dose tacrolimus (26%) at three years posttransplant (13). Finally, cyclosporine and corticosteroids seem to have an additive

effect in raising cholesterol, and withdrawing steroids only partially improves cholesterol levels of transplant recipients (14).

On the other hand, mTOR inhibitors lead to a significant increase in both cholesterol and TG, in a dose-dependent pattern possibly through a decrease in the catabolism of apolipoprotein B_{100}, inhibition of insulin and insulin-like growth factor signals, and/or alterations in hepatocyte synthesis of lipid moieties (15). Among the other available immunosuppressive agents, there is no data suggesting that either mycophenolic acid (MPA) or azathioprine causes clinically significant increases in any lipid fraction.

Despite the potential role of immunosuppressants in the etiology of posttransplant dyslipidemia, it is important to exclude secondary causes of elevated lipids such as hypothyroidism, diabetes, excessive alcohol intake, chronic liver disease, nephrotic syndrome and other medication-induced dyslipidemias (i.e. atypical antipsychotics, oral estrogen, protease inhibitors).

Treatment of Dyslipidemia in Transplantation

The 2004 Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for managing dyslipidemia considered RTR a high-risk group that carries a CHD risk-equivalent (16). General screening recommendations are to check lipid profiles within six months of transplant, at 1-year posttransplant, and annually thereafter (16) with repeat testing two to three months after a change in treatment or with the development of other conditions known to worsen dyslipidemia. Current target lipid levels in transplant recipients have been extrapolated from the general population (16) and are shown in Table 1.

Common agents used for treatment of dyslipidemia include statins, fibric-acid derivatives (fibrates), nicotinic acid (niacin), ezetimibe and bile-acid sequestrants. The statins are the most commonly prescribed antilipemic medications based on strong evidence that they reduce LDL cholesterol and cardiovascular events with excellent

Table 1: Management of dyslipidemia in transplant recipients (modified from Ref. [16])

Dyslipidemia	Goal	Initiate	Increase	Alternative
TG>500 mg/dL with LDL <100 mg/dL	TG<500 mg/dL	TLC	TLC + niacin	Fibrate or statin
LDL 100–129 mg/dL	LDL< 100 mg/dL	TLC	TLC + low-dose statin (7,18)	Ezetimibe or niacin
LDL>130 mg/dL	LDL<100 mg/dL	TLC + low-dose statin (7,18)	TLC + 50% max dose statin	Ezetimibe or niacin
TG>200 mg/dL and non-HDL>130 mg/dL	Non-HDL <130 mg/dL	TLC + low-dose statin	TLC + 50% max dose statin	Ezetimibe or niacin

TG = triglycerides; LDL = low-density lipoprotein; HDL = high-density lipoprotein; therapeutic lifestyle changes (TLC) Non-HDL: TC minus HDL (surrogate for increased remnant lipoproteins in the setting of high TG); max. = maximum. To convert mg/dL to mmol/L, multiply triglycerides by 0.001129, and cholesterol by 0.02586.

Table 2: Statin antilipid strength and conversion doses

Atorva statin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	% ↓ in LDL-C
–	40 mg	20 mg	1 mg	20 mg	–	10 mg	30%
10 mg	80 mg	40 mg	2 mg	40 mg	–	20 mg	38%
20 mg	–	80 mg	4 mg	80 mg	5 mg	40 mg	41%
40 mg	–	–	–	–	10 mg	80 mg	47%
80 mg	–	–	–	–	20 mg	–	55%
–	–	–	–	–	40 mg	–	63%

tolerability (6). Statins are competitive inhibitors of HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. By blocking HMG-CoA reductase, statins reduce intracellular cholesterol in the liver and stimulate the expression of LDL receptors, increasing receptor-mediated endocytosis of LDL; thereby, lowering serum LDL and TC. Additional effects include a mild reduction in TG and a modest elevation in HDL. Other than their antilipemic effects, statins also have pleiotropic effects that may contribute to their cardiovascular benefits, including anti-inflammatory properties and modulation of endothelial function (17).

There has only been a single prospective randomized trial in transplant recipients comparing statins (fluvastatin) with placebo (ALERT trial), which showed a 35% reduction in the incidence of nonfatal myocardial infarctions (MIs) or cardiac deaths in statin-treated patients (p = 0.005) (18). Though this trial involved more than 2,000 RTR with a 5-year follow-up, fluvastatin only showed a nonsignificant reduction in the primary composite endpoint of cardiac death, nonfatal MI or coronary intervention compared to placebo (RR 0.83, 95% CI 0.64–1.06, p = 0.139). This observation was likely secondary to the underpowered nature of this trial for the chosen primary endpoint in patients with stable graft function and no significant prior cardiovascular disease (18). Moreover, the use of a low-potency statin that only decreases cholesterol by approximately 30% might also help explain the results, since more intensive lowering of LDL has been shown to bring additional cardiovascular benefits (6). Nonetheless, an extension of the ALERT trial with 1,652 patients from the original study reinforced the prior findings, demonstrating a 21% reduction of a major cardiac event (p = 0.036) and a 29% reduction in cardiac death or definite nonfatal MI (p = 0.014). However, there was no difference in graft survival between the groups (7). The safety profile of fluvastatin was comparable to placebo when co-administered with cyclosporine, with no difference in documented hepato- or myo-toxicities.

Tolerability and Safety of Statins

Although statins share a similar mechanism of action, they differ with respect to potency (Table 2), metabolism and frequency of adverse events. Elevated liver function tests (LFTs) may occur in 1–3% of patients in a dose-dependent pattern with spontaneous resolution occurring in 70% of cases, even if the statin is continued. Statin-induced severe liver dysfunction or liver failure is extremely rare. Nevertheless, monitoring of LFTs is warranted after statin initiation or when doses are changed. If LFTs are higher than three-times the upper limit of normal without any other potential explanations, statin discontinuation or dose reduction is recommended. Most centers would consider reintroduction of a different statin at a lower dose after documentation of resolution of transaminitis.

Statin-induced myopathy has a variable presentation, including isolated muscle pain or weakness, elevated creatinine phosphokinase (CK) or rhabdomyolysis. The prevalence of these conditions is 1–3%, 0.1% and 0.005%, respectively (19). Myopathy risk seems to be elevated in the elderly, patients with a glomerular filtration rate (GFR) <30 ml/min, those receiving maximum statin doses and in patients taking medications or foods that inhibit the cytochrome-P450 CYP3A4 or CYP2C9 isoenzymes (16,19–21) (Table 3). Although both tacrolimus and cyclosporine are known inhibitors of CYP3A4 enzyme *in vitro* (22), recent reports suggest that cyclosporine results in a stronger inhibitory effect of the enzyme *in vivo* when compared to tacrolimus (23), which could explain the higher association of cyclosporine with statin-related toxicities in clinical trials (16). In addition, cyclosporine has a dominant inhibitory effect on a liver-specific transporter of

Table 3: Common inhibitors of cytochrome P450 isoenzymes

CYP3A4 inhibitors	CYP2C9 inhibitors
Amiodarone	Amiodarone
Azole antifungals (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole)	Antidepressants (fluoxetine, fluvoxamine)
Cimetidine	Azole antifungals
Cyclosporine	Antibiotics (metronidazole, TMP/SMX)
Gemfibrozil	Omeprazole
Grapefruit	Zafirlukast
Macrolide antibiotics (erythromycin, chlarithromycin)	
Nefazodone (antidepressant)	
Non-dihydropyradine calcium channel blockers (diltiazem, verapamil)	
Protease inhibitors (ritonavir, indinavir, nelfinavir, saquinavir, etc.)	

statin (OATP1B1), blocking its entry into hepatocytes and leading to higher levels of systemic statin. Simvastatin, atorvastatin and lovastatin are primarily metabolized by the CYP3A4 isoenzyme and are especially susceptible to drug–drug interactions with known inhibitors of these enzymes, carrying a potential risk of elevation of serum statin levels and subsequent acute toxicities (Table 3). Conversely, pravastatin, pitavastatin, fluvastatin and rosuvastatin have alternative metabolic pathways and do not carry a similar risk of drug–drug interactions (21). It should be noted that studies comparing concurrent use of pravastatin and cyclosporine with pravastatin alone indicate that concurrent use results in significantly higher circulating levels of pravastatin (24,25). The mechanism of the drug–drug interaction appears to be mediated through P-glycoprotein inhibition. This same interaction has not been shown to exist between tacrolimus and pravastatin. However, when assessing the clinical impact of this drug–drug interaction, three studies in RTR and one study in heart transplant recipients taking both pravastatin and cyclosporine found no association with rhabdomyolysis (26–29).

The FDA recently issued a warning concerning the disproportionate increase in myopathy associated with high-dose simvastatin, based on a comprehensive data review from the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), other larger clinical trials of high-dose statins and the agency's Adverse Event Reporting System (AERS). The SEARCH trial was a double-blind randomized trial involving 12,064 MI survivors who were treated with either simvastatin 20 mg/day or 80 mg/day with a mean follow-up of 6.7 years (30). There was no significant difference in the incidence of major cardiovascular events between the groups; however, mild myositis developed in 53 patients in the 80-mg group (0.9%), but in only two patients in the 20-mg group (0.03%). Rhabdomyolysis occurred in 22 patients in the 80-mg group (0.4%) but in no patients in the 20-mg group. Among the available statins on the market, simvastatin appears to be particularly prone to drug–drug interactions, in part because it is extensively metabolized by CYP3A4. Additional data from large clinical trials also corroborated the above findings, suggesting that the incidence of myositis is very low for all statins, but is approximately three times as high with the 80 mg dose of simvastatin compared with rosuvastatin or atorvastatin (31). Finally, FDA analysis of the AERS database also reported a higher rate of fatal rhabdomyolysis with 80 mg of simvastatin compared with 80 mg of atorvastatin or 40 mg of rosuvastatin (31).

Amlodipine is most commonly used antihypertensive agent in renal transplantation. Compared to diltiazem and verapamil, amlodipine is considered a weak inhibitor of the CYP3A4 isoenzyme. Though the potential of an interaction with simvastatin exists (32), most literature has not shown a significant correlation of amlodipine with statin-induced myotoxicity by itself (33). Nonetheless, the FDA decision to recommend avoiding doses higher than 20 mg of simvas-

tatin in patients receiving amlodipine is reasonable since it conveys the general message of potential toxicities with higher doses of simvastatin.

Rosuvastatin has recently been associated with increased proteinuria and renal failure at higher doses in a post-marketing report from the FDA (34). This would be of special concern in RTR. The findings from the Prospective Evaluation of Proteinuria and Renal Function in Diabetic and Non-Diabetic Patients with Progressive Renal Disease trials, which have compared atorvastatin 80 mg/day with rosuvastatin 10 or 40 mg/day in dyslipidemic patients with moderate proteinuria, should help provide further insight into this potentially serious adverse event. Until these results are published, it is reasonable to limit rosuvastatin to the lowest recommended doses.

General Recommendations for Dyslipidemia Management in Renal Transplantation

The following recommendations have been adapted from 2004 K/DOQI guidelines, which were incorporated in the 2009 KDIGO clinical practice guidelines for the management of RTR. Taking into account the most recent literature on the matter and the FDA-issued warning on simvastatin, we detail some suggestions for managing dyslipidemia in RTRs (Table 1).

Elevated LDL-cholesterol
LDL levels have a direct correlation with cardiovascular events; therefore, aggressive management of the high-risk population, including organ transplant recipients, should be a major focus of posttransplant care. Mild elevations of LDL (100–129 mg/dL) should be initially managed with therapeutic lifestyle changes (TLC), including diet, exercise and weight reduction (16). An emphasis on dietary incorporation of plant sterols, soy protein, viscous fibers and nuts has been recently shown to decrease LDL by more than 12% (35). There have been no randomized trials in the transplant population testing the efficacy of TLC and conclusions have been extrapolated from the general population. Nonetheless, increased physical activity has been linked to decreased overall and cardiovascular-related mortality in transplant recipients and should be strongly encouraged (36).

In patients with LDL above 100 mg/dL after TLC, a low-dose statin should be initiated (Table 1). The dose should be titrated to achieve LDL goal (<100 mg/dL) while minimizing adverse reactions. The safest statins to use are fluvastatin, pravastatin and pitavastatin, which are not metabolized by cytochrome P450 3A4. These statins are of lower potency and should likely be selected in patients with mild LDL elevations and low cardiovascular risk factors. Table 2 shows the LDL-lowering efficacy of different statins and their respective conversion doses. Extrapolating recent data from the general population, a meta-analysis from 26

randomized trials including more than 170,000 participants provided evidence that more intensive statin therapy can further reduce major cardiovascular events by 15% (95% CI 11–18; $p < 0.0001$) (6). Therefore, a more potent statin, like atorvastatin, may be a more appropriate choice for transplant recipients, since it has well-documented effectiveness in decreasing cardiovascular events in the general population, powerful antilipemic effects, excellent tolerability in combination with tacrolimus and presumed beneficial effects in decreasing proteinuria (6,23).

For statins metabolized by cytochrome P450, maximal doses should not exceed 50% of the general maximal recommended dose and additional agents that inhibit the hepatic cytochrome P450 enzymes should be avoided or used with extreme caution (Table 3). Even though tacrolimus was not included on the FDA's warning regarding simvastatin, it is reasonable to follow similar recommendations and limit the maximal dose of simvastatin to no more than 40 mg daily or 20 mg if in combination with amlodipine in tacrolimus-treated patients. Based on preliminary results revealing that rosuvastatin may increase the risk of proteinuria and renal failure, it is reasonable to limit rosuvastatin to its lowest dose (5 mg) and possibly avoid in RTR until more data are available.

In transplant recipients who develop minor adverse effects on a statin, dose reduction is indicated, although conversion to a different statin may be necessary. In refractory cases, the use of second-line agents, like ezetimibe or niacin, should be considered. Due to the hyperlipidemic effects of immunosuppressive medications, dose reductions, or discontinuation of the offending immunosuppressant could be considered in severe cases of dyslipidemia refractory to pharmacotherapy. However, practitioners must weigh the risk of rejection versus the risk of cardiovascular disease. Tapering of prednisone or conversion from cyclosporine to tacrolimus has been shown to successfully improve the lipid profile; however, other metabolic side effects might arise from these changes, such as diabetes in the case of tacrolimus (37).

Hypertriglyceridemia
Fasting-elevated TG above 500 mg/dL leads to an increased risk of pancreatitis which should be initially managed with TLC, including diet, weight reduction, increased physical activity, abstinence from alcohol and treatment of hyperglycemia, if present. If TLC is not sufficient to reduce TG to <500 mg/dL and LDL level is at goal, then treatment with niacin should be considered (38). Possible side effects with niacin include flushing, pruritus and nausea. If patient is intolerant to niacin, fibrates could be the third line of therapy based on its side effects' profile. Fibrates are peroxisome proliferator activated receptor-α agonists and

are effective agents at decreasing TG; however, they have been associated with elevations in creatinine (more common with fenofibrate) and with significant myositis when used in combination with statins (more common with gemfibrozil; Table 3) (39). Fenofibrate is also predominantly metabolized in the kidneys and dose adjustments are necessary in renal dysfunction. According to the National Kidney Foundation (NKF) guidelines, gemfibrozil is considered the fibrate of choice. Recently, the National Lipid Association (NLA) has recommended gemfibrozil dosage adjustments during renal dysfunction, including a 50% reduction in dose in patients with a GFR of <60 ml/min/1.73 m^2, and avoidance of all fibrates in patients with a GFR of <15 ml/min/1.73 m^2. In cases where severe hypertriglyceridemia is secondary to sirolimus or everolimus, decreasing dose or discontinuation of the agent should be considered.

In patients with moderately elevated TG (200–499 mg/dL), measurement of non-HDL cholesterol levels is recommended to guide therapy (40). Non-HDL cholesterol is calculated as TC minus HDL cholesterol and it represents mostly remnants of VLDL, which is a good predictor of cardiovascular disease (41). Elevated non-HDL cholesterol in combination with high TG is a common pattern in patients with metabolic syndrome, which has been shown to be an independent risk factor for cardiovascular events in transplant recipients and is also associated with greater risk of new-onset diabetes, graft loss and mortality (42). Therefore, a non-HDL >130 mg/dL in the setting of hypertriglyceridemia should trigger the initiation of a low-dose statin as first-line therapy (Table 1), since the ultimate goal of dyslipidemic management is to reduce cardiovascular events and the best evidence, to date, favors statin-therapy.

Adding a second lowering agent to a statin
The addition of ezetimibe could be considered in patients with persistently elevated LDL despite statin therapy. Ezetimibe is a selective inhibitor of the intestinal absorption of cholesterol at the brush border. In nontransplant recipients with CKD, the combination of ezetimibe with low-dose simvastatin (20 mg) was able to safely reduce the incidence of major cardiovascular events compared to placebo (RR 0.83, 95% CI 0.74–0.94; p = 0.0021) (8). In two small retrospective trials in RTR, ezetimibe has been shown to effectively decrease TC and TG while maintaining an excellent safety profile (43,44). Nonetheless, the effect of ezetimibe on morbidity and mortality of transplant recipients is unknown.

Fibrates can efficiently reduce TG and LDL and raise serum HDL (Table 4); however, their use has been associated with increased risk of myotoxicity, in particular when gemfibrozil was coadministered with statins (19) (Table 3). This effect is not seen with fenofibrate and is related to the inhibition of the glucuronidation pathway involved in the metabolism

Table 4: Lipid-lowering medication review

Medication class/generic name	Typical dosing regimen	Dosing instructions	Major adverse events/drug–drug interactions
Statins (HMG CoA reductase inhibitors)			
Atorvastatin	10–80 mg/day	May be given any time of the day	Headache; nausea; sleep disturbance; elevations in hepatocellular enzymes and alkaline phosphatase. Myositis and rhabdomyolysis, primarily when given with gemfibrozil or cyclosporine; myositis is also seen with severe renal insufficiency (CrCl <30 mL/min). Most statins can also affect digoxin metabolism and levels.
Fluvastatin	20–80 mg/day Sustained Release = 80 mg/day	Regular release should be administered at bedtime or be given twice daily if dose >40 mg/day	
Lovastatin	20–80 mg/day	Should be administered with the evening meal. Should be dosed twice daily if dose >20 mg/day	
Pitavastatin	1–4 mg/day	May be given any time of the day	
Pravastatin	10–80 mg/day	Should be administered at bedtime	
Rosuvastatin	5–40 mg/day	May be given any time of the day	
Simvastatin	10–80 mg/day	Should be administered at bedtime	
Fibric acid derivatives (fibrates)			
Gemfibrozil	600 mg twice daily	30 to 60 min before meals	Skin rash, gastrointestinal (nausea, bloating, cramping), myalgia; lowers blood cyclosporine levels; potentially nephrotoxic in cyclosporine treated patients. Avoid in patients with CrCl <30 mL/min.
Fenofibrate	Nanocrystal 145 mg/day Micronized 160–200 mg/day	Micronized taken with meals. Use lower doses with renal insufficiency.	
Bile acid sequestrants			
Cholestyramine	4–24 g/day	Take within 30 min of a meal. A double dose with dinner produces same lipid-lowering effect as BID dosing.	Nausea, bloating, cramping and constipation; elevations in LFTs. Impaired absorption of fat soluble vitamins, digoxin, warfarin, thiazides, β-blockers, thyroxine and phenobarbital. Avoid use with MPA.
Colestipol	5–30 g/day	Same as cholestyramine	
Colesevalem	3.75 g/day	Take with meals daily or divided BID	
Cholesterol absorption inhibitors			
Ezetimibe	10 mg/day	May be given any time of the day	Increased transaminases in combination with statins
Miscellaneous			
Nicotinic acid	1–6 g/day	Given with meals. Start with 100 mg BID and titrate to 500 mg TID. After 6 weeks, check lipids, glucose, liver function and uric acid. Increase dose as needed.	Prostaglandin-mediated cutaneous flushing, headache, warm sensation and pruritus; hyperpigmentation (particularly in intertriginous regions); dry skin; nausea; vomiting; diarrhea and myositis
Omega-3-acid ethyl esters	4 g/day (supplement); or 2 servings per week of oily fish	May be given any time of the day	Nausea and GI upset (eructation)

of statins (39). Fibrates have also been associated with significant decline in renal function in patients with CKD (45). Lastly, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke in patients with type 2 diabetes, as compared with simvastatin alone in the ACCORD trial (46). Similar to other trials (FIELD and HHS) (47,48), there was a possible benefit in the subgroup of patients with elevated TG and low HDL. Nonetheless, we believe that fibrates should be generally avoided in RTR until further data on efficacy and safety are provided.

Niacin could be considered an adjuvant agent to help decrease LDL after maximization of statin therapy. However, there are no published data on the safety and efficacy of combination therapy with a statin and niacin in transplant recipients. A recent trial suggested that in nontransplant patients with atherosclerotic disease and an LDL cholesterol level below 100 who are also on a statin (+/– ezetimibe), the addition of niacin to optimize HLD and TG does not lead to any clinical benefit (49). Therefore, it seems prudent at this time to use niacin alone in patients intolerant to statins with suboptimal LDL control. Lastly, bile acid sequestrants are effective at reducing LDL by binding to bile acids in the intestine and interrupting their reabsorption. They have been shown to be effective in combination with statins; however, their use is often limited by gastrointestinal adverse events and their potential impairment in the absorption of coadministered medications, including some immunosuppressants (e.g. MPA products). Bile acid

sequestrants should be avoided in any transplant recipient receiving MPA due this drug–drug interaction.

Conclusions

Cardiovascular disease is the leading cause of mortality among RTR and it accounts for a significant amount of death with a functioning allograft. Despite possible adverse events, statins are the agents of choice in RTR and pravastatin, fluvastatin and pitavastatin appear to be ideal statins based on their reduced potential for drug misadventures. However, given their low-potency, a high-potency statin, such as atorvastatin, may be necessary in patients with significant hyperlipidemia. Future trials should better evaluate the safety and efficacy of adjuvant agents in this specific population.

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