The Efficacy and Safety of the 3-Hydroxy-3-methylglutaryl-CoA Reductase Inhibitors in Chronic Kidney Disease, Dialysis, and Transplant Patients

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Summary

Coronary heart disease (CHD) is the leading cause of death in Western civilizations, in particular in chronic kidney disease (CKD) patients. Serum total cholesterol and LDL have been linked to the development of atherosclerosis and progression to CHD in the general population. However, the reductions of total and LDL cholesterol in the dialysis population have not demonstrated the ability to reduce the morbidity, mortality, and cost burden associated with CHD. The patients at greatest risk include those with pre-existing CHD, a CHD-risk equivalent, or multiple risk factors. However, data in the dialysis population are much less impressive, and the relationship between plasma cholesterol, cholesterol reduction, use of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, and reduction in incidence of CHD or effect on progression of renal disease have not been proven. Adverse event information from published trials indicates that agents within this class share similar tolerability and adverse event profiles. Hepatic transaminase elevations may occur in 1 to 2% of patients and is dose related. Myalgia, myopathy, and rhabdomyolysis occur infrequently and are more common in kidney transplant patients and patients with CKD. This effect appears to be dose related and may be precipitated by administration with agents that inhibit cytochrome P-450 isoenzymes. Caution should be exercised when coadministering any statin with drugs that metabolize through cytochrome P-450 IIIA-4 in particular fibrates, cyclosporine, and azole antifungals. Elderly patients with CKD are at greater risk of adverse drug reactions, and therefore the lowest possible dose of statins should be used for the treatment of hyperlipidemia.

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Introduction

Coronary heart disease (CHD) afflicts over 16.5 million Americans and is the leading cause of death in Western civilizations. Approximately 500,000 deaths are related to coronary heart disease in the United States every year. In 2009, the American Heart Association estimated the cumulative direct and indirect cost burden of CHD in the United States at $400 billion, which continues to escalate annually. The role of serum cholesterol in the development of atherosclerosis and progression to CHD is unequivocal. The correlation between elevated serum LDL cholesterol as a risk factor for development of CHD has been firmly established. In both the Framingham Heart Study (1) and the Multiple Risk Factor Intervention Trial (2), an increased serum-cholesterol level was linked to an increased rate of coronary heart disease. In addition, it has been shown that reduction of LDL cholesterol reduces morbidity and mortality in patients with and without CHD. In light of this evidence, the National Cholesterol Education Program Kidney Disease Outcomes Quality Initiative and the American Diabetes Association have developed management guidelines for cholesterol reduction. Current recommendations for primary and secondary prevention advocate maintenance of LDL cholesterol <100 mg/dl in patients with underlying CHD, atherosclerosis, or diabetes (3–5). In patients without these underlying comorbidities, LDL recommendations are <130 or <160 mg/dl, based upon the number of individual risk factors present (6).

The most common agents for the treatment of hyperlipidemia include fibric-acid derivatives, nicotinic acid, bile-acid sequestrants, and 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors or statins. Statins are the most commonly prescribed agents for the treatment of hypercholesterolemia. The popularity of these agents in the treatment of hypercholesterolemia reflects their efficacy in reducing LDL and their excellent tolerability and safety. Clinical trials with statins in non-chronic kidney disease (CKD) patients with and without coronary heart disease and with and without high cholesterol have consistently demonstrated reductions in the relative risk of major coronary events by 30%, with greater absolute benefit in patients with higher baseline risk. Although the statins share a similar mechanism of action and side-effect profile, they differ with respect to potency, availability of various strengths, dosage forms, and cost. The withdrawal of cerivastatin from the market because of toxicity, the warning letter from the Food and Drug Administration regarding the po-

tential for serious drug interactions with statins, and new data from three recent clinical studies have questioned the efficacy of these drugs in primary prevention in chronic kidney disease and dialysis patients. This review will attempt to address some of the questions that have been raised regarding the safety and efficacy of these drugs in chronic kidney disease, kidney transplant recipients, and the dialysis population.

Pharmacology

All of the currently available HMG-CoA reductase inhibitors primarily inhibit hepatic cholesterol biosynthesis through inhibition of HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in the hepatic biosynthesis of cholesterol. *In vitro* data also support the activity of these drugs at the receptor level through up-regulation of LDL receptors. The net effect after administration is primarily exhibited as reductions in serum total cholesterol and LDL cholesterol, modest reductions in serum triglycerides (TG), and modest elevations in serum HDL. These effects are thought to be the primary characteristics associated with the attenuation of progression of atherosclerosis and the reduction in clinical events in patients with coronary artery disease, which have been observed with these drugs in clinical trials (Table 1).

Treatment with HMG-CoA reductase inhibitors has been shown to produce beneficial effects at the endothelial level, displayed by atherosclerotic plaque stabilization and in some cases plaque regression, and at the clinical level exhibited by reduction in cardiovascular and cerebrovascular events (7). Numerous clinical trials have demonstrated the beneficial effect of these agents in reducing levels of circulating cholesterol and morbidity and mortality associated with atherosclerotic heart disease. A summary of some of the crucial clinical-outcome trials with these agents is highlighted below and in Table 1.

Pharmacokinetics

The pharmacokinetic properties of the individual statins are listed in Table 2 (8). Lovastatin has poor absorption with a bioavailability of 20%. The presence of food increases oral absorption. Lovastatin undergoes extensive first-pass metabolism, and only 5% of the oral dose reaches systemic circulation. Biliary excretion is the primary route of elimination, with only 10% of the absorbed dose excreted in the urine. The overall absorption rate of pravastatin is similar to lovastatin with a bioavailibility of 17% after oral administration. Unlike other statins, pravastatin is more hydrophilic and is metabolized via hydroxylation processes. The overall protein binding of pravastatin is significantly lower compared with other statins. The most significant difference with atorvastatin and rosuvastatin compared with other statins is a longer half-life (9,10). This accounts for the greater potency of these agents and the lack of preferred dosing at bedtime (with other statins, bedtime dosing is preferred because cholesterol biosynthesis undergoes a circadian cycle, with the majority of cholesterol formation occurring while an individual is asleep). Most statins are metabolized via the through P-450 III A4 and P-450 2C8 enzyme systems. All of the statins should be used with caution in patients with impaired renal function, particularly elderly patients with impaired renal function taking drugs that are metabolized through P-450 III-A4. Elderly patients are at greater risk of adverse drug reactions including myopathy and rhabdomyolysis for several reasons (11). Decreased muscle mass and renal function may increase total drug exposure of statins in the elderly with chronic kidney disease. In addition, comorbid conditions such as osteoarthritis and back pain can mask the early signs and symptoms of myopathy and rhabdomyolysis. Because gemfibrozil inhibits the P-450 enzyme system, the increased area under the curve of statins in the presence of gemfibrozil should be expected (12). This drug-drug interaction and other patient factors may explain the high incidence of myopathy observed with this combination. The overall incidence of drug interactions with a combination of statins and fenofibrate is less than that reported with statins and gemfibrozil. However, fenofibrate may increase creatinine production and cause an increased serum creatinine value. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, a lower estimated GFR, lower creatinine clearance, and higher serum creatinine were reported in the fenofibrate group compared with the control group (13). However, the elevation of serum creatinine and cystatin C was noted without any changes to tubular function (14).

Statins in CKD

CHD, as previously stated, is the leading cause of death in Western civilizations, in particular in patients with CKD. Some risk factors for CHD include elevated triglycerides and total cholesterol along with decreased HDL cholesterol. The pathophysiology of dyslipidemia in CKD is not well understood, but dyslipidemia tends to worsen as GFR declines. Liu *et al.* (15) demonstrated that in a subset of dialysis patients without evidence of systemic inflammation or malnutrition, elevated cholesterol is an independent risk factor for cardiovascular mortality. As compared with the general population, as CKD progresses, the relationship of dyslipidemia and CHD risk and cardiovascular outcomes is unclear. Lipid profiles are dynamic along the spectrum of CKD to end-stage renal disease (ESRD) and kidney transplant recipients (Table 3). The increasing level of triglycerides seems to correlate with decreasing renal function (16), but once a patient reaches ESRD, the greatest cardiovascular risk lies rather in the patients with lower cholesterol levels, presumably because there is coexisting malnutrition and increased low-grade inflammation. This uremic milieu (oxidation and glycation of lipoproteins and chronic low-grade inflammation) also likely contributes to the development of atherosclerosis and therefore a higher risk of death. It is unlikely that high cholesterol levels confer a protective effect in ESRD patients, and the mechanism by which inflammation and malnutrition confounds the association between total-cholesterol and cardiovascular outcomes is unclear (7). In contrast, the renal transplant recipient typically shows a progressive relationship between lipid levels and coronary artery disease events, mirroring the pattern seen in the general population. It is for these reasons that assessment of cardiovascular risk in CKD, ESRD, and renal transplant recipients can be difficult. Other risk factors for cardiovas-

Table 1. Summary of outcome studies of statins in high-risk patients, dialysis, and kidney transplant recipients

Name of author	Year	*n*	Interventions	Results
Primary intervention				
Shepherd *et al.* (75)	1995	6595	Pravastatin (40 mg/d) *versus* placebo	A 22% reduction in the risk of mortality[a]
Downs *et al.* (76)	1998	6605	Lovastatin (20 to 40 mg daily) *versus* placebo	Lovastatin reduces the risk for the first acute major coronary event.[a]
Colhoun *et al.* (77)	2004	2838	Atorvastatin (10 mg daily) *versus* placebo	Atorvastatin reduced the mortality rate by 27%.[a]
Ridker *et al. et al.* (78)	2008	17,802	Rosuvastatin (20 mg/d) *versus* placebo	Rosuvastatin significantly reduced the incidence of major cardiovascular events in patients with high sensitivity C-reactive protein levels[a]
Secondary and interventions				
4S Study (79)	1994	4444	Simvastatin on mortality and morbidity in patients with CAD	A 30% reduction in the risk of mortality[a]
LIPID Study (80)	1998	9014	Pravastatin (40 mg/d) *versus* placebo in patients with CAD	Mortality: 6.4% in pravastatin group *versus* 8.3% in placebo group[a]
HPS study (55)	2002	20,536	Simvastatin (40 mg/d) *versus* placebo in patients with CAD or high risk	24% reduction in cardiovascular events[a]
CARE study (81)	1996	4159	Pravastatin (40 mg/d) *versus* placebo post-MI	24% reduction in mortality rate[a]
IDEAL study (82)	2010	999	Atorvastatin (80 mg/d) *versus* simvastatin (20 to 40 mg/d)	A primary endpoint occurred at 44.7% in the simvastatin group *versus* 37.9% in the atorvastatin group[a]
MIRACL study (83)	2001	3086	Atorvastatin (80 mg/d) *versus* placebo	A primary endpoint occurred at 14.8% in the atorvastatin group *versus* 17.4% in the placebo group.[a]
Pitt *et al.* (84)	1999	341	Atorvastatin (80 mg/d) *versus* angioplasty	Incidence of ischemic events was 36% lower in the atorvastatin group over an 18-month period.[a]
Dialysis population				
Wanner *et al.* (4D) (41)	2004	1255	Atorvastatin (20 mg/d) *versus* placebo	Atorvastatin lowered the LDL level but had no significant effect on primary endpoint.
Fellstrom *et al.* (AURORA) (42)	2009	2776	Rosuvastatin (10 mg/d) *versus* placebo	Rosuvastatin lowered the LDL level but had no significant effect on primary endpoint; CAD, coronary artery disease.
SHARP (36)	2010	9438	Simvastatin/ezetimide (20/10 mg) *versus* placebo	Simvastatin/ezetimide lowered the LDL level but had no significant effect on primary endpoint in dialysis patients.
Kidney transplantation Holdaas *et al.* (57)	2005	1052	Fluvastatin (40 mg/d) *versus* placebo	Fluvastatin (40 mg) lowered LDL, but no significant mortality benefits[a], reduced cardiovascular events

[a]Significantly better than control arm; CAD, coronary artery disease.

cular mortality include: obesity, smoking, diabetes, hypertension, male gender, and family history of CHD. The National Cholesterol Education Program and National Kidney Foundation have established guidelines for cholesterol management on the basis of patient risk factors. Patients at greatest risk include those with pre-existing CHD

Table 2. Pharmacokinetic properties of currently available statins (23)

Drug	Bioavailability	Excretion	$t_{1/2}$ (hours)	Major Metabolites	Protein Binding	Effects of Renal/Hepatic Impairment
Atorvastatin (Lipitor®)	Extensively absorbed ~14% absolute bioavailability after first pass metabolism via CYP3A4	Metabolized <2% urine	14	Ortho and para-hydroxylated derivatives (active)	>98%	Plasma levels not affected by renal disease; increased plasma levels with severe liver disease
Fluvastatin (Lescol®)	98% absorbed ~24% absolute bioavailability after first pass via CYP2C9	Metabolized <6% urine, ~90% fecal	<1	Hydroxylated metabolites (active, do not circulate systemically)	>89%	Increased plasma levels with severe liver disease
Lovastatin (Mevacor®)	35% absorbed <5% absolute bioavailability after first pass via CYP3A4	Metabolized 10% urine, 83% fecal	3 to 4	b-Hydroxyacid; 6-hydroxy derivative and other metabolites	>95%	Increased plasma levels with severe liver disease
Pravastatin (Pravacol®)	34% absorbed ~17% absolute bioavailability after first pass metabolism	Metabolism/renal 20% urine, 70% fecal	1.8	3α-Hydroxy isomeric metabolite	>50%	Increased plasma levels with severe renal and liver disease
Rosuvastatin (Crestor®)	20% absorbed ~8% absolute bioavailability after first pass metabolism	Metabolism/renal 10% urine, 90% fecal	20.8		>88%	Increased plasma levels with severe renal and liver disease
Simvastatin (Zocor®)	60 to 80% absorbed <5% absolute bioavailability after first pass via CYP3A4	Metabolism/renal 13% urine, 60% fecal	3	β-Hydroxy acid; 6-hydroxy-methyl derivatives	>95%	Increased plasma levels with severe renal and liver disease

Table 3. Dyslipidemia in CKD patients (relative to the general population) (7)

	Predialysis	Hemodialysis	Kidney Transplant
Total cholesterol	Normal	Normal or decreased	Increased
HDL	Decreased	Decreased	Decreased
LDL	Normal or decreased	Normal or decreased	Increased
VLDL	Increased	Increased	Increased
Triglycerides	Increased	Increased	increased

The information is adopted and modified from reference 86.

or the presence of a CHD-risk equivalent and those individuals with multiple risk factors (Table 3). One guideline suggests that renal insufficiency in and of itself be considered a CHD-risk equivalent (14,17). In addition to the traditional risk factors associated with the development and progression of CHD, the prevalence of hypertension and left ventricular hypertrophy increases as GFR declines (18). The National Kidney Foundation has published guidelines for managing dyslipidemias in adults with CKD (Table 4).

Studies have shown that statins may have multiple pleiotropic effects. Aside from their significant cholesterol-lowering effects, statins seem to have other benefits: reduction of urinary protein excretion and inflammation and reduction of fibrosis of tubular cells, thereby potentially improving renal function (19). Lipids have also been shown to directly affect gomeruli in rat experimental models. Grone *et al.* (20) demonstrated that rats fed a high-cholesterol and high-fat diet exhibited a significantly higher number of glomeruli with sclerotic foci as compared with those rats on a low-fat, cholesterol-free diet. Patients with CKD are found to have increased levels of parathyroid hormone, calcium-phosphate products (markers of vascular calcification), as well as elevated levels of inflammatory markers such as C-reactive protein and homocysteine, all of which are considered surrogate markers of advancing CHD. Total and LDL cholesterol levels are higher in patients with nephrotic-range proteinuria as compared with those patients with lower levels of proteinuria. It is for these reasons that it would be logical to aggressively treat dyslipidemia early in the CKD patient because the benefits of statin therapy on the spectrum to advanced CKD and ESRD are decreased if at all present.

The Treating to New Targets (TNT) study suggested that by reducing LDL cholesterol or by other effects of atorvastatin, progression of renal disease as well as cardiovascular risk were reduced (21). This study showed a slower rate of decline in renal function that was dose-related in patients with an estimated GFR of >60 ml/min. The Pravastatin Pooling Project combined data from patients with renal impairment from three randomized trials (CARE, LIPID, and WOSCOPS) that were initially conducted on the general population (22). This subgroup consisted of worldwide patients with GFR between 30 and 90 ml/min with varying CKD pathology. This study showed an independent association of an increased risk of myocardial infarction, coronary death, or percutaneous/surgical coronary revascularization among those patients with moderate CKD. Of the CKD patients on statins, there was an associated risk reduction of 20% in the composite outcome over 5 years, similar to the effect seen in patients without CKD. In contrast, a prospective study by Muntner *et al.* (22a) did not show that treating dyslipidemia decreased cardiovascular mortality in the CKD population, despite a prediction of the opposite.

Proteinuria and hypertension are known to accelerate the decline in GFR. BP control and reduction of proteinuria reduce the rate of decline of GFR as evidenced by the GUARD study (23). Statins have been shown to reduce proteinuria in rat experimental models that may have implications on the progression of renal disease in humans. Rayner *et al.* (24) showed that in rats fed a high-cholesterol

Table 4. Cholesterol targets based on patient risk category (85)

Patient Category	Target LDL Level	Initiation Level (mg/dl)		Risk Stratification (Total Cholesterol in non-CHD)	
		Diet	Drug	Cholesterol	Classification
Primary prevention				<130 mg/dl	Desirable
no CHD and <2 Risk factors[a]	160 mg/dl	≥160 mg/dl	≥190 mg/dl	130 to 159 mg/dl	Borderline high
no CHD and ≥2 risk factors[a]	130 mg/dl	≥130 mg/dl	≥160 mg/dl	≥160 mg/dl	High
Secondary prevention					
CHD or CHD risk equivalent[b]	100 mg/dl	>100 mg/dl	≥130 mg/dl		

[a]Risk factors for CHD include: age male ≥45, female ≥55; family history of CHD: first-degree relative with MI or sudden cardiac death, male relative age <55, female relative age <65; current cigarette smoker; hypertension, BP ≥140/90 mmHg or on antihypertensive; diabetes mellitus.
[b]CHD risk equivalents: diabetes, other atherosclerotic disease, and multiple risk factors that confer high long-term risk.

diet, the severity of hypercholesterolemia was correlated with proteinuria, and the number of gomeruli with lipid deposits was significantly increased. A study by Bianci *et al.* (25) suggested that statin therapy may reduce proteinuria in humans. This randomized trial demonstrated that patients with proteinuria (without evidence of systemic disease known to cause glomerulonephritis) taking atorvastatin had a significant reduction in urinary protein excretion and a slower decline in creatinine clearance as compared with those patients on no treatment. The study by Grone *et al.* (20) mentioned earlier showed that rat glomerular sclerosis and nephron loss was less pronounced in rats on a high-fat diet but protected against arterial hypertension. This provided further evidence that glomerular hemodynamic factors play an important role in the development of glomerular sclerosis with a lipid-rich diet. Lee *et al.* (26) demonstrated that pravastatin significantly reduced proteinuria as compared with placebo in patients with well-controlled hypertension and proteinuria but without hyperlipidemia. The reduction of proteinuria was independent of cotreatment with an angiotensin receptor blocker, but there was no difference in serum creatinine levels or creatinine clearance observed between the two groups. A study comparing simvastatin to cholestyramine in hypertensive type 2 diabetic patients showed a similar reduction in lipid levels, but only those patients on simvastatin therapy had a significant reduction in urinary albumin excretion and a slower rate of decline of GFR. This study appeared to demonstrate a renoprotective effect independent of reduction in lipid levels. It should be noted that some statins (especially rosuvastatin) have been shown to increase proteiuria, but this effect was mild and transient, of tubular origin, and usually observed at high doses (27), and there were no negative effects on renal function (28).

Statins have been proven to be safe and well-tolerated by the majority of patients, but this class of drugs is not entirely free of adverse drug reactions (29). Patients with CKD are at increased risk of these adverse effects and should be monitored carefully for tolerability and toxicity. Although there is little published data, Kidney Disease Outcomes Quality Initiative (KDOQI), in accordance with Adult Treatment Panel III, recommends dosage reductions of several of the statins to approximately 50% in patients with stage IV or V CKD. The dosage recommendations are outlined in Table 5 (4).

Two new studies, Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease PLANET I (n = 325) and PLANET II (n = 220), enrolled patients with urinary protein/creatinine ratios of 500 to 5000 mg/g and a fasting LDL-cholesterol level of 90 mg/dl or higher (30,31). The patients were stable on and had used angiotensin-converting–enzyme inhibitors or ARBs for at least 3 months before enrollment. The patients were randomized to atorvastatin at 80 mg/d, rosuvastatin at 10 mg/d, and rousvastatin at 40 mg/d. In PLANT I, atorvastatin was associated with a significant reduction on proteinuria by approximately 20%, but there was no effect on the rate of decline of GFR, whereas rosuvastatin worsens GFR by 8 ml/min per year but has no effect on proteinuria. A similar result was noted in the PLANT II study (31). The incidence of common renal adverse

Table 5. National Kidney Foundation guidelines for managing dyslipidemias in adults with CKD (5)

Dyslipidemia	Goal	Initiate	Increase	Alternative
TG (>500 mg/dl)	TG (<500 mg/dl)	TLC	TCL + fibrate or niacin	Fibrate or niacin
LDL-C (100 to 129 mg/dl)	LDL-C (<100 mg/dl)	TLC	TCL + low dose statin	Bile-acid sequestrant or niacin
LDL-C (>130 mg/dl)	LDL-C (<100 mg/dl)	TCL + low dose statin	TCL + maximum-dose statin	Bile-acid sequestrant or niacin
TG (>200 mg/dl) and non-HDL-C (>130 mg/dl)	Non-HDL-C (< 130 mg/dl)	TLC + low dose statin	TCL + maximum-dose statin	Fibrate or niacin

This table was published in the American Journal of Kidney Diseases (Suppl. 3) and modified. KDOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease (copyright by the National Kidney Foundation, 2003) were followed. HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TCL, therapeutic lifestyle changes.

reactions observed was higher with the use of rousvastatin compared with other statins (32,33) (Table 6).

A recent Cochrane Review (having 99% of the weight of the summary estimate from the Pravastatin Pooling Project) of statins for patients with CKD but not on dialysis found that among 26 studies comparing statins and placebo, statins significantly reduced total, LDL-cholesterol, and triglyceride levels, although there was no significant change in the level of HDL cholesterol (34). There was also a significant reduction in all-cause and cardiovascular deaths, as well as nonfatal cardiovascular events with statin use in comparison with placebo. There were no significant differences in adverse effects in CKD patients on statins compared with those on placebo (35). Only a small number of studies had adequate data to show that statins reduce protein excretion. There was no significant difference in the change in creatinine clearance with statins in comparison with placebo, suggesting that renoprotective effects cannot be confirmed. In addition, this antiproteinuric effect of statins on the eventual need for renal replacement therapy is still unclear (34). There was no difference found in the withdrawal rates caused by adverse events; there was also no significant increase in the risk of rhabdomyolysis or abnormal liver function with statins in comparison with placebo. Several studies are ongoing to answer some of these questions. The results of the Study of Heart and Renal Protection (SHARP) study recently were presented (36). The SHARP study compared the efficacy and safety of 20 mg of simvastatin and 10 mg of ezetimibe daily *versus* placebo in patients with chronic kidney disease (median estimated GFR of 27 ml/min) at increased risk for cardiovascular disease. This study was a prospective, randomized, controlled study spanning 380 centers and 18 countries. Simvastatin/ezetimibe administration was blinded. The study included approximately 9500 patients (6245 patients with chronic kidney disease and 3023 patients on dialysis) with similar baseline characteristics in each treatment arm that were followed for a median of 4.9 years. The objective of this study was to evaluate the efficacy and safety of combination therapy of antilipidemic agents to prevent cardiovascular complications and events in patients with chronic kidney disease, in addition to assessing the outcome of cholesterol reduction on the progression of renal function and the need for renal replacement therapy.

The primary efficacy outcome was major vascular events defined as fatal and nonfatal myocardial infarction, cardiac death, fatal and nonfatal stroke, or revascularization. Inclusion criteria consisted of documentation of chronic kidney diseases defined as plasma or serum creatinine greater than or equal to 1.7 mg/dl in men or greater than or equal to 1.5 mg/dl in women or patients who were receiving dialysis (hemodialysis or peritoneal dialysis), aged greater than or equal to 40 years. The exclusion criteria were: definite history of myocardial infarction or coronary revascularization procedure, renal transplantation, past medical history significant for chronic liver disease or abnormal liver function, clinical evidence of active muscle-skeleton disease, or previous history of adverse drug reaction to a statin or to ezetimibe. The patients were assessed at 2 and 6 months and every 6 months thereafter, with each patient followed for at least 4 years. For the primary efficacy outcome, the rate of cardiovascular events was 15.1% with the treatment arm and 17.6% in the placebo arm (risk reduction = 0.83; 95% confidence interval, 0.74 to 0.94; $P = 0.0022$).

The treatment arm was statistically superior to the placebo arm of the study. However, the overall simvastatin and ezetimibe therapy did not significantly reduce the relative risk of coronary mortality, any cardiac mortality ($P = 0.38$), death from stroke or any vascular death ($P = 0.30$), or all-cause cardiovascular death ($P = 0.65$). In dialysis patients there was a slight and insignificant reduction of relative risk in all cardiovascular events with the simvastatin and ezetimibe group compared with placebo arm (15% *versus* 16.5%). For safety outcomes, no increase of cancer (9.4% *versus* 9.5%), liver function abnormalities (0.6% *versus* 0.6%), hepatitis (0.5% *versus* 0.4%), or end-stage renal disease progression (33.9% *versus* 34.6%) was noted in the treatment arm compared with placebo, respectively.

The study has several important strengths: a large number of patients with chronic kidney disease, multicenter and multinational results, and some positive evidence for most patients with chronic kidney disease. However, the primary limitation of the study is that one-third of the patients were nonadherent to this treatment, and no overall benefits in regard to cardiac and vascular mortality benefits were noted after 5 years of treatment. In addition less than 1%/year benefit for fatal and nonfatal cardiovascular complications in dialysis population has limited practical implications. Complete release information from this study will be informative. Finally, the study did not include a control arm with simvastatin alone; therefore, the SHARP study cannot provide the evidence that combination of simvastatin with ezetimibe is more effective than simvastatin alone. Previously, in the ENHENCE study (Effect of Ezetimibe Plus Simvastatin *versus* Simvastatin

Table 6. PLANET I: Summary of renal adverse events (%)

Adverse event	10 mg/d Rosuvastatin ($n = 116$)	40 mg/d Rosuvastatin ($n = 123$)	80 mg/d Atorvastatin ($n = 110$)	*P*
Any renal adverse event	7.8	9.8	4.5	NS
Acute renal failure	0.0	4.1	0.9	<0.05
Serum creatinine doubling	0.0	4.9	0.0	<0.01
Serum creatinine doubling or acute renal failure	0.0	7.3	0.9	<0.01

The information in the table is adapted from Heart.org.

Alone on Atherosclerosis in the Carotid Artery), despite decreases in levels of LDL cholesterol and C-reactive protein, combined therapy with ezetimibe and simvastatin did not show clinically or statically significant differences in changes in intima-media thickness, as compared with simvastatin alone (37). Taylor and coworkers (38) also reported on the ARBITER 6-HALTS trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies) that addition of ezetimibe was no more effective compared with niacin in decreasing the progression of carotid intima-media thickness in patients receiving statin therapy (Table 7).

The Statins in Proteinuric Nephropathies (ESPLANADE) study assessed the effect of fluvastatin plus angiotensin-converting–enzyme inhibitors or angiotensin II receptor blockers in reducing proteinuria in patients with CKD and diabetic nephropathy (39). Patients were randomized to fluvastatin *versus* placebo and were followed for 6 months. The starting dose of fluvastatin was 40 mg daily; the dose was increased to 80 mg daily after 1 month of treatment. Each arm of the study included less than 90 patients with a very short length of follow-up. A small numerical decrease in proteinuria was noted in fluvastatin-treated patients, but differences between groups were not clinically or statistically significant. Although the overall renal benefit was not noted in the SHARP study, the Lipid lowering and Onset of Renal Disease (LORD) study might help to clarify the benefits of statins on slowing the progression of kidney disease in patients with continuum of chronic kidney disease as well as the requirement of ESRD management (40).

Table 7. Summary of relative risk reduction in SHARP study

Endpoint	Events (%)		Relative Risk	95% Confidence Interval	Endpoint Definition in the Trial
	Studied treat.	Control treat.			
cardiovascular event (fatal and nonfatal)[a]	701/4650 (15.1%)	814/4620 (17.6%)	0.87	[0.79; 0.95]	Major vascular event
All cause death	1142/4650 (24.6%)	1115/4620 (24.1%)	1.02	[0.95; 1.09]	
End stage renal disease	1057/4650 (22.7%)	1084/4620 (23.5%)	0.97	[0.90; 1.04]	
Coronary event	213/4650 (4.6%)	230/4620 (5.0%)	0.92	[0.77; 1.10]	
Cancer	438/4650 (9.4%)	439/4620 (9.5%)	0.99	[0.87; 1.12]	Any cancer incident

The information in the table is adapted from www.trialresultscenter.org.
[a] $P = 0.0022$.

Use of Statins in Dialysis Patients

Liu *et al.* (15) initially investigated the relationship between cholesterol level and mortality in patients undergoing dialysis and accounting for inflammation and malnutrition. The patient population consisted of 823 patients recently initiated on dialysis. The patients were recruited from 81 clinics between 1995 and 1998 and were followed for 2.4 years. The patients were classified into two groups: those with and those without inflammation and malnutrition. The markers of inflammation and malnutrition in the study were serum albumin, <3.6 mg/L; C reactive protein, >10 mg/L; and IL-6, >3.09 pg/ml. Achievement of any of the three marker cutoff points was grounds for inclusion into the inflammation and malnutrition group. Cholesterol measurements were reported as total-cholesterol and non-HDL cholesterol levels. Mortality was classified into two categories: all-cause or cardiovascular disease (CVD) mortality. CVD mortality encompassed death from CHD, cerebrovascular accident (including hemorrhage), peripheral vascular disease, atherosclerotic heart disease, mesenteric infarction, or sudden death when CVD is present. An inverse association was noted for inflammation and cardiovascular death. In this study, an inverse association was noted because of the cholesterol-lowering effects of inflammation, not because of any protective effect of high cholesterol levels and supported aggressive cholesterol lowering treatment.

In the 4D study (Die Deutsche Diabetes Dialyze Studie), type 2 diabetic patients who had been receiving hemodi-

alysis for more than 2 years were randomized in a multicentered, double-blinded, placebo-controlled prospective study in two arms of placebo or atorvastatin (41). The objective of this study was to ascertain the efficacy and safety of statin therapy on modulating CVD morbidity and mortality in dialysis patients. The groups were adequately matched in terms of baseline characteristics. Of the 1255 patients entering the study, 619 were assigned to the atorvastatin group (with 77.1% completing the study protocol), and 636 to the placebo group (with 76.1% completing the study protocol). At randomization, the median LDL level in the atorvastatin group was 121 mg/dl, dropping to 72 mg/dl after 4 weeks of treatment, a 42% reduction. The placebo group had a median LDL level of 125 mg/dl at baseline, which decreased to 120 mg/dl 4 weeks later. Cumulative incidence of the primary outcome was 12.6% at 1 year and 31.9% at 2 years for the atorvastatin group and 11.2 and 30.5% for the placebo group at 1 and 2 years, respectively (NS; $P = 0.37$). This study demonstrated that in patients who are on hemodialysis with type 2 diabetes who have a baseline cholesterol level between 80 and 190 mg/dl, treatment with statins did not reduce the rate of cardiac vascular death, nonfatal myocardial infarction (MI), nonfatal stroke, or all-cause death.

The AURORA study was an international, multi-centered, randomized, placebo-controlled, double-blinded, prospective trial in ESRD patients between the ages of 50 and 80 who had been on maintenance hemodialysis for at least 3 months (42). The objective of the study was to evaluate the efficacy and safety profile of statin therapy in patients undergoing hemodialysis. The mean duration of follow-up was 3.2 years, and the mean duration of exposure to rosuvastatin (20 mg daily) was 2.4 years. The 2776 patients who were eligible were randomized to one of two groups: rosuvastatin (20 mg) or placebo. The two groups were matched well for baseline characteristics. In the rosuvastatin group, at the 3-month mark, LDL, total cholesterol, TG, HDL, and C reactive protein were all changed from baseline by 42.9% ↓, 26.6% ↓, 16.2% ↓, 2.9% ↑, and 11.5% ↓, respectively. In the placebo group, the same changes were as follows: 1.9% ↓, 0.5% ↓, 0.9% ↑, 0.8% ↑, and 3.8% ↑ respectively. The primary endpoint occurred in 396 rosuvastatin patients and 408 placebo patients, generating an insignificant effect of active treatment with a hazard ratio of 0.96 (0.84 to 1.11) and $P = 0.59$. Like the 4D study, a marginal increase in hemorrhagic stroke in the treatment group was noted.

As mentioned previously, the SHARP study did not show any significant mortality or cardiovascular event benefits in dialysis population (36). It is important to emphasize that cardiovascular disease in hemodialysis is multifactorial: it is not just the LDL level that contributed to this increase. Phosphate, calcium medium atherosclerosis, parathyroid hormone, BP, and anemia play integral pathophysiological roles in cardiovascular morbidity and mortality in hemodialysis patients (9,43).

Statins in Renal Transplant Recipients

As in the CKD and ESRD populations, cardiovascular disease is the leading cause of mortality in the kidney transplant population, accounting for over 30% of deaths with a functioning allograft (44). Dyslipidemia is a significant risk factor in the development of coronary heart disease. It has been demonstrated previously that patients with hypercholesterolemia and hypertriglyceridemia have decreased long-term graft survival overall compared to those without hypercholesterolemia (45). Because the goal of renal transplantation is the maximization of both kidney recipient and allograft survival, heart disease risk factor modification becomes important for the postkidney transplant population.

Changes to the lipid profile of transplant patients are listed in Table 3 noted previously. As found by Kimak *et al.* (46), the lipid profile of transplant patients include an elevated total cholesterol, triglyceride level, LDL, non-HDL, triglyceride rich lipoproteins, apoB, apoCIII, and decreased HDL levels. This is in part due to already existing dyslipidemia from progressive CKD in this population. However, dyslipidemia is also due to both patient- and transplant-specific factors, including the medications used for prevention of transplant rejection. Bittar *et al.* (47) found that cholesterol and triglyceride abnormalities were more pronounced in transplanted women compared with transplanted men and an age-matched general population. Previously described are findings that corticosteroids, cyclosporine, age, and total serum cholesterol before transplant were independently related to elevated cholesterol levels post-transplantation (47). In addition, it also appears that the combination of cyclosporine and corticosteroids were additive in their effects in raising cholesterol levels post-transplant (48). When withdrawing the corticosteroids, the cholesterol levels improved. Investigators have found in animal models that cyclosporine leads to decreased hepatic cholesterol 7-α-hydroxylase and decreased adipose and skeletal muscle cell lipoprotein lipase. This leads to increased hypercholesterolemia and hypertriglyceridemia caused by decreased cholesterol and triglyceride catabolism and clearance (49). It also binds to the LDL receptor causing increased levels. Corticosteroids increase the enzymatic action of free fatty acid synthetase and acetyl-CoA carboxylase, which leads to increased production of triglycerides, VLDL, and LDL and decreased production of HDL.

In comparison with cyclosporine, tacrolimus has less effect on raising cholesterol levels. A previous study evaluated the physiologic and metabolic changes with conversion of cyclosporine to tacrolimus. After conversion, patients' total cholesterol, triglycerides, and LDL all decreased within 6 months of conversion, whereas HDL remained stable (50). The number of patients remaining on statins did not change. Others found similar results, with lower rates of hypercholesterolemia in patients on tacrolimus compared with patients on cyclosporine (51,52). Studies by Wissing *et al.* (53,54) reported that the conversion of cyclosporine to tacrolimus led to a decrease in total-cholesterol and LDL levels and that the addition of atorvastatin to either cyclosporine or tacrolimus significantly improved these levels equally. When evaluating transplant patients on target of rapamycin inhibitors sirolimus and everolimus, it was found that they had higher rates of hyperlipidemia compared with those not on these medications. In addition, the increases in cholesterol levels did appear to be dose dependent.

Although immunosuppressive agents have the side effect of increased hyperlipidemia, they are necessary in preventing

Table 8. Statin dosages for dyslipidemias in patients with chronic kidney disease

Drug	CKD Stage			
	1 to 2	3	4 to 5	Transplant
Atorvastatin	10 to 80 mg	10 to 80 mg	10 to 80 mg	10 to 20 mg
Fluvastatin	20 to 80 mg	20 to 80 mg	10 to 80 mg	10 to 40 mg
Pravastatin	20 to 80 mg	20 to 40 mg	10 to 20 mg	10 to 40 mg
Rosuvastatin	10 to 40 mg	10 to 20 mg	5 to 10 mg	5 mg
Simvastatin	20 to 80 g	10 to 40 mg	10 to 20 mg	5 to 20 mg

The information in the table is adopted and modified from reference 4.

allograft rejection. Given that transplant patients require immunosuppressive agents, post-transplant management of dyslipidemia includes treatment for these lipid abnormalities similar to the general population with diet, exercise, and medication. Most of the data related to pharmacologic agents for the management of hyperlipidemia after transplantation are derived from studies and data from the general population, which did not specifically note participation by transplant patients (55,56). Given their effectiveness in the general population, there have been efforts to study these drugs specifically in the transplant population.

The ALERT (Assessment of LEscol in Renal Transplantation) study was a clinical investigation of the safety and efficacy of statins in renal transplant recipients. 2102 patients were randomized to fluvastatin or placebo and were followed for 5 years. The fluvastatin treatment was associated with lower LDL cholesterol concentrations by 32%; however, fluvastatin did not reduce the rates of coronary intervention procedures or mortality (57). In an extension of the ALERT study, in 1652 after 6.7 years, the mean LDL-cholesterol was 98 mg/dl compared with a prestudy level of 159 mg/dl in patients randomized to fluvastatin. The overall risk of Major Adverse Cardiovascular Events was reduced by 21% ($P = 0.036$), and a 29% reduction was shown in cardiac death or definite nonfatal myocardial infarction ($P = 0.014$). However, the total mortality and graft loss did not differ significantly between groups (58,59).

More recently, ezetimibe has been used in post-transplant patients whose hypercholesterolemia has been difficult to control on statin therapy. Several of these studies have shown that ezetimibe is useful in decreasing cholesterol, LDL, and triglyceride levels as monotherapy or in combination therapy with statins (60–63). Renal function, creatine kinase (CK), liver enzymes, and calcineurin inhibitor levels remained stable with ezetimibe use (60,62,63). The previously discussed studies involving statins and ezetimibe were limited by their small number of patients.

Wissing *et al.* (54) found that endothelial function, when measured using flow-mediated brachial-artery dilation, improved significantly with atorvastatin added to cyclosporine compared with conversion to tacrolimus alone or tacrolimus with atorvastatin. There has been evidence that statins may also have other effects in addition to their lipid-lowering properties. These properties include an anti-inflammatory effect, an immunological effect that is beneficial to transplant grafts, stimulation of cells involved in ischemic repair, increased nitric oxide production, stabilization of atherosclerotic plaques, and prevention of plaque rupture (64).

Tolerability and Safety

Cumulative information derived from published clinical trials indicate that the HMG-CoA reductase inhibitors have an excellent safety record and a favorable risk/benefit profile, with a low risk of significant adverse events (<1% incidence) (65). Adverse event information from published trials indicates that these agents share similar tolerability profiles. Although individual

Table 9. Common inhibitors of the P450 CYP3A4 and CYP2C9 enzyme systems

CYP3A4 Inhibitors			CYP2C9 Inhibitors
Amiodarone	Fluvoxamine	Nelfinavir	Amiodarone
Cannabinoids	Grapefruit juice	Norfloxacin	Azole antifungals
Clarithromycin	Indinavir	Propoxyphene	Chloramphenicol
Cyclosporin	Itraconazole	Quinine	Cimetidine
Danazol	Ketoconazole	Ritonavir	Fluoxetine
Delevirdine	Omeprazole	Saquinavir	Fluvastatin
Diltiazem	Metronidazole	Sertraline	Fluvoxamine
Erythromycin	Mibefradil	Troleandomycin	Metronidazole
Fluconazole	Miconazole	Verapamil	Omeprazole
Fluoxetine	Nefazodone	Zafirlukast	Ritonavir
			Sulaphenazole
			TMP/SMX

TMP/SMX, Trimethoprim/Sulfamethoxazole.

trials may have reported differences in tolerability of specific agents, comparative trials have been unable to distinguish significant differences in tolerability between agents (66). From large individual trials, the discontinuation rates for lovastatin and simvastatin were 3 and 6%, respectively (67). For all statins, the overall risk of rhabdomyolysis is less than 0.5% in the general population. This risk may be higher in patients with chronic kidney disease, the elderly, and patients taking other drugs or foods that inhibit CYP3A4, specifically grapefruit, cyclosporine, azole antifungals, macrolide antibiotics, and fibrates. Myopathy is the major adverse effect of the statins and is defined as muscle pain or weakness associated with elevation of CK levels higher than 10 times the upper limit of normal. Myopathy in patients on statin monotherapy occurs in approximately 0.1% of patients and is dose related. Symptoms may include fever and malaise, and cases have been associated with elevated serum statin drug levels. Potentially fatal rhabdomyolysis is a rare complication of treatment with the statins. Rhabdomyolysis and acute renal failure may result if myopathy is not recognized, and the drug is continued. If the drug is discontinued and the myopathy is recognized promptly, it is reversible, and acute kidney injury is unlikely to ensue (68). Rhabdomyolysis is a clinical and biochemical syndrome resulting from an injury that damages the integrity of the sarcolemma of skeletal muscle, leading to the release of potentially toxic muscle cell components into the circulation. Although myopathy and serum elevations of creatine kinase frequently precede rhabodmyolysis, myopathy rarely progresses to rhabdomyolysis.

Rhabdomyolysis was not reported in any of the clinical trials with the statins, but postmarketing surveillance indicated a much higher rate with cerivastatin (withdrawn from market) compared with other agents. This side effect may be precipitated by concomitant administration with agents that inhibit cytochrome P-450 isoenzymes. Caution should be exercised when coadministering any statin with gemfibrozil, cyclosporine, erythromycin or clarithromycin, azole antifungals, high doses of niacin, protease inhibitors, or the antidepressant nefazodone. Spontaneous adverse event reporting to the World Health Organization suggests that the incidence of this event is similar for all of the currently available statins.

Mechanism of Statin-induced Myotoxicity

A variety of hypotheses have been proposed to try to explain the myotoxic effects of statins. The following are some of the mechanisms that have been suggested: statin-induced interruption of glycoprotein synthesis in the muscle membrane, deficiency in chloride channel activation in the muscle membrane, and increased intracellular calcium concentrations leading to impaired membrane function (69). Membrane lipids are in a constant dynamic with plasma cholesterol levels. Membrane fluidity is a function of its cholesterol composition. Statins lower plasma lipids, which in turn lowers the membranes' cholesterol composition, resulting in probable damage to the cell. Other proteins within the membrane such as the Na/K channels may also be negatively affected by a decrease in fluidity.

Table 10. Comparative efficacy of currently available statins on lipids and lipoproteins

						Mean Change in Lipid and Lipoprotein Levels			
Rosuvastatin (Crestor®)	Atorvastatin (Lipitor®)	Simvastatin (Zocor®)	Lovastatin (Mevacor®)	Pravastatin (Pravacol®)	Fluvastatin (Lescol®)	Total	LDL	HDL	Triglycerides
0.5	1	2	4	4	8				
		5 mg	10 mg	10 mg	20 mg	−17%	−21%	NR	−5 to −10%
	5 mg	10 mg	20 mg	20 mg	40 mg	−22%	−27%	+4 to 8%	−10 to −15%
5 mg	10 mg	20 mg	40 mg	40 mg	80 mg	−27%	−34%	+4 to 8%	−10 to −20%
10 mg	20 mg	40 mg	80 mg			−32%	−41%	+4 to 8%	−15 to −25%
20 mg	40 mg	80 mg				−37%	−48%	+4 to 8%	−20 to −30%
40 mg	80 mg					−42%	−55%	+4 to 8%	−25 to −35%

Relative potency of individual agents (in decreasing order with smaller numbers reflecting the higher potency agent), doubling the dose increases efficacy by 8 to 10%.

Muscle injury causes the release of CK, the enzyme responsible for the breakdown of ATP. Acute muscle necrosis as seen in rhabdomyolysis leads to the depletion of ATP reserves, which are required to maintain the myocytes' integrity. Statins may also inhibit the production of mitochondrial ATP, predisposing the cell to disruption. Another possible mechanism is that statins can decrease serum levels of coenzyme Q_{10}, an essential electron carrier in the mitochondrial respiratory chain, although statins have not been shown to reduce coenzyme Q_{10} levels in skeletal muscle.

Hepatotoxicity

Hepatocellular necrosis and hepatoxicity induced by statins are considered a myth (70). In a study of 100,000 statins user over 2.5 years, no case of acute hepatitis was reported among statin users (71). Asymptomatic hepatic transaminase elevation (less than three times the upper limit of normal) may occur in 1 to 2% of patients on an HMG-CoA reductase inhibitor and in general is dose related. In most patients, elevation of transaminase enzymes is resolved spontaneously with continued therapy, although discontinuation may be required in some patients. It is typically recommended that if liver function tests are three times the upper level of normal, the use of statins should be discontinued (67). No specific statins appears to have a greater likelihood to produce elevation of transaminase compared with other agents in the class (67). In a large study (n = 20,536) of simvastatin compared with placebo, transaminases elevations was noted in 0.7% of the simvastatin group and in 0.6% of the placebo group (55). A similar finding has been reported with other statins (29). Transaminase elevation typically returns to normal after 2 to 3 months after discontinuation (72). In lieu of these effects, monitoring of serum transaminases at 6- and 12-week intervals after the initiation of therapy and every 6 months thereafter is recommended with the HMG-CoA reductase inhibitors (73).

Drug Interactions

Atorvastatin, cerivastatin, lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme of the cytochrome P-450 enzyme system, whereas fluvastatin is primarily metabolized by the CYP2C9 isoenzyme. Concomitant administration of these agents with known inhibitors of these enzymes (Table 8) carries the potential for acute drug toxicity caused by elevations in serum concentrations. Pravastatin undergoes minimal hepatic metabolism and therefore carries a reduced potential for toxicity secondary to drug-drug interactions (74).

Dosing and Administration

For the general population, the approved dosage range, recommended starting dose, and typical dose utilized, along with any specific dosing considerations for each of the statins, are listed in Table 9. As noted, lovastatin is the only agent in which administration with food is recommended, whereas evening administration is recommended with all of the available agents except atorvastatin. Simvastatin (20 mg/d) should be considered the drug of choice for most patients with chronic kidney disease. Pravastatin is the most suitable agent for transplant patients to achieve target cholesterol levels because of a reduced risk of drug interactions. The typical effect of a specific dose of an individual statin on an individual's lipid profile is illustrated in Table 10.

Summary

The HMG-CoA reductase inhibitors (statins) are the current drugs of choice for the treatment of hypercholesterolemia. All of the available statins effectively lower total cholesterol and LDL cholesterol, modestly lower triglycerides, and have a moderate effect in increasing HDL cholesterol. Clinical trials with the statins indicate that these drugs consistently reduce the risk for major coronary events in people with coronary heart disease, with varying levels of baseline cholesterol. It is generally hypothesized that the benefit of treatment with these drugs is a reflection of the global risk of the patient and the baseline LDL level in the population studied. The ability of a particular agent to lower cholesterol is a reflection of the dose used and the respective potency of the individual agent. Atorvastatin and rosuvastatin have demonstrated the greatest potency of the available agents in cholesterol reduction but are the most expensive agents too. Simvastatin is less expensive, but there is a higher rate of drug interactions at the highest dose. Simvastatin (20 mg/d) should be considered the drug of choice for most patients with chronic kidney disease. Pravastatin and fluvastatin are the most suitable agents for transplant patients to achieve target cholesterol levels because of the reduced risk of drug interactions. As a class, statins are well tolerated, and with the exception of rosuvastatin, there are no known differences in safety. The effective comparativeness of statins for the primary prevention in dialysis has not been demonstrated. Given their demonstrated efficacy and safety record coupled with our understanding that statins may produce benefits through cholesterol reduction and via lipid-independent mechanisms, these agents should be used in the management of patients with established coronary artery disease. However, they should be used with caution for primary prevention of cardiovascular in dialysis patients who are at great risk of toxicity and drug interactions.

Disclosures

None.

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