Is Lipid Control Necessary in Hemodialysis Patients?

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Although high serum total cholesterol and LDL cholesterol levels are predictive of cardiovascular diseases in the general population, this association is more complex in the dialysis patients. Two recent randomized trials failed to show significant beneficial effects of statins on the primary cardiovascular outcomes in these patients. The reasons for this lack of benefits are unclear. The postulates include the possibilities that LDL cholesterol is not important in atherogenesis and that atherosclerosis is not a major contributor to cardiovascular diseases in the dialysis population. It is important to note that high serum LDL cholesterol level is not a prominent feature of uremic dyslipidemia. Instead, the hallmark dyslipidemias in the dialysis population are hypertriglyceridemia as a result of the accumulation of lipoprotein remnant particles, low serum HDL cholesterol levels, high serum levels of lipoprotein(a) [Lp(a)], and the modification of LDL cholesterol by oxidation and carbamylation. *In vitro* and epidemiologic studies have further suggested that these abnormal lipoproteins or aberrant serum lipoprotein levels are atherogenic. More research efforts should be directed toward these dyslipidemic states and the multitude of other putative cardiovascular risk factors in dialysis patients.

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Hypercholesterolemia as a Cardiovascular Risk Factor in the General Population

Hypercholesterolemia is a well-established cardiovascular risk factor in the general population. The available literature, however, has suggested that the relationship of serum total cholesterol level with mortality and cardiovascular events in the long-term dialysis population is different (1). This article is a limited review on serum lipids in the general population and the results of two recent randomized trials on statins on clinical outcomes in hemodialysis patients, followed by considerations for clinical practice based on the interpretation of these data by the author.

In the Multiple Risk Factor Intervention Trial (MRFIT), the risks for 6-yr mortality associated with serum total cholesterol levels were analyzed in 361,662 men aged 35 to 57 yr (2). Above the serum cholesterol level of 181 mg/dl, coronary heart disease mortality increased progressively, with a relative risk (RR) of 3.8 in men with cholesterol levels >253 mg/dl. The risk seemed to decrease with lowering of serum cholesterol to levels below approximately 140 mg/dl. This landmark epidemiologic study has formed a sound basis for many subsequent randomized trials to lower serum cholesterol, especially during the statin era. In a meta-analysis of 164 trials, various preparations of statins lowered serum total cholesterol levels by 30 to 60% or a mean of 70 mg/dl (3). Concomitant to this reduction in serum total cholesterol levels was a substantial reduction in the risk of ischemic heart disease by 60% in a meta-analysis of 58 trials.

Pharmacotherapy using serum LDL cholesterol level as the target also shows beneficial clinical effects of statins. In the meta-analysis of 14 randomized trials on statins performed by the Cholesterol Treatment Trialists, all-cause mortality and major vascular events decreased respectively by 12 and 21% during a mean follow-up period of 5 yr for each 1-mmol/L (38.67-mg/dl) decrease in serum LDL cholesterol level (4). The lowest LDL cholesterol target that is associated with the best outcome, however, has not been well defined. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) study compared intensive therapy using atorvastatin and moderate therapy using pravastatin in 1825 patients after acute coronary syndrome (5). Reduction of serum LDL cholesterol to levels below the usual target of 80 to 100 mg/dl was associated with further improvement in clinical outcomes. Indeed, the group with achieved LDL cholesterol <40 mg/dl fared the best, with a 39% reduction in the primary end point. Thus, there is a compelling case for lowering serum total cholesterol and LDL cholesterol using pharmacotherapy, especially statins, in the general population.

It is interesting that most of the clinical benefit of lowering serum LDL cholesterol levels seems to be achieved after 3 to 5 yr of statin therapy (3,4); no further decrease in cardiac events can be seen after continued treatment for longer durations (3). Thus, with a decrease in serum LDL cholesterol level >55 mg/dl, the risk reduction in ischemic heart disease was approximately 33% after 1 to 2 yr, 50% after 3 to 5 yr, and 52% after >6 yr of treatment. If this beneficial effect of statins were also applicable to the dialysis population, then it should be seen well within the life expectancy of many of these patients who lived >5 yr. Thus, the notion that dialysis patients do not live long enough to benefit from chronic cardiovascular risk reduction therapies does not seem to be legitimate.

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Observational Studies of Hypercholesterolemia in the Dialysis Population

Chronic kidney disease (CKD) represents a very wide spectrum of GFRs and proteinuria, associated with highly variable rates and risk factors for cardiovascular events. As might be expected, the coronary risk factors for individuals with stage 1 or 2 CKD are generally quite similar to those without kidney disease (6). In contrast, a number of epidemiologic studies (1,7,8) and a few randomized clinical trials (9–11) have shown unconventional associations of putative cardiovascular risk factors with clinical outcomes in long-term dialysis patients. The first large observational study relating serum cholesterol levels and clinical outcomes was published in the early 1990s, based on the database of National Medical Care (1). In that study, a U-shape relationship between serum total cholesterol level and the risk for all-cause mortality was observed, with the lowest risk found in the category with cholesterol levels between 200 and 250 mg/dl. Cholesterol levels between 250 and 300 mg/dl seemed to be associated with a modest increase in mortality risk, but the subgroup with cholesterol levels <100 mg/dl had a three-fold increase in mortality risk after adjustment for case mix. The high risk for this latter category has been attributed by many investigators to malnutrition. According to this hypothesis, low serum total cholesterol is a marker of protein-energy malnutrition; the latter is a predictor or harbinger of death.

Subgroup analysis of the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study by Liu *et al.* (12) is compatible with this hypothesis. In that analysis, 823 incident dialysis patients were classified by the presence or absence of inflammation and/or malnutrition (defined as low serum albumin levels or elevated serum levels of C-reactive protein or IL-6). Mean serum total cholesterol level was indeed lower in the presence of inflammation/malnutrition than in its absence. Consistent with the results derived from the National Medical Care database, an increase in baseline serum cholesterol level was associated with a decreased risk for all-cause mortality in the entire CHOICE cohort. This seemingly paradoxically inverse relationship between serum cholesterol and mortality was also observed in patients with inflammation/malnutrition. In contrast, in patients without inflammation/malnutrition, high serum cholesterol level was associated with an increased mortality risk. These observations in general seem to support the notion that the inverse association of total cholesterol level with mortality in dialysis patients is due to the cholesterol-lowering effect of systemic inflammation/malnutrition and not to a protective effect of high cholesterol concentrations. Nonetheless, in the subgroup with inflammation/malnutrition, the lower mortality risk in patients with high cholesterol levels (>240 mg/dl), compared with those with lower cholesterol levels, is difficult to understand. It is reckoned that the sample size of this particular subgroup was small, thereby increasing the chance of spurious results.

The superior clinical outcomes associated with statin therapy for hypercholesterolemia in the general population (3), including those with type 2 diabetes (13), provide a powerful argument for using the same approach in CKD, which is generally regarded as a state of very high cardiovascular risks (14). Indeed, it has been well established that statins are very effective in lowering serum total and LDL cholesterol in patients with various stages of CKD, including those who are on long-term dialysis (10,11,15). The efficacy of statins in reducing cardiovascular events and mortality, however, may differ depending on the stage of CKD. Subgroup analysis of large randomized trials has shown that statins reduce cardiovascular events in patients with stage 3 CKD (15). The efficacy in long-term dialysis patients seems to be different. Two retrospective analyses of the US Renal Data System Wave 2 (16) and the Dialysis Outcomes and Practice Patterns Study (DOPPS) (17) showed that the use of a statin was associated with decreased risk for death from cardiovascular causes in dialysis patients. Two recent randomized trials, however, showed seemingly different results from these observational studies, as discussed next.

4D Trial

Die Deutsche Diabetes Dialyse Studie (4D) targeted German patients who had type 2 diabetes and ESRD and were on long-term hemodialysis (10), two conditions each engendering substantial cardiovascular risks. In that multicenter, double-blinded trial, 1255 patients were randomly assigned to atorvastatin or placebo. The primary end point was a composite of death from cardiac causes, nonfatal myocardial infarction, and stroke. Serum LDL cholesterol decreased rapidly in 4 wk by 42% among patients who received atorvastatin (20 mg/d), confirming the pharmacologic efficacy of statin in this population. Despite this reduction in cholesterol, during a median follow-up period of 4 yr, the decrease in primary the end point associated with atorvastatin was not statistically significant (RR 0.92; 95% confidence interval [CI] 0.77 to 1.10; $P = 0.37$).

There are several potential interpretations of this seemingly negative result. First, LDL cholesterol may not be important in the pathogenesis of cardiovascular disease in dialysis patients. This hypothesis could, in turn, be explained by the postulate that LDL cholesterol is not important in atherogenesis in these patients. Alternatively, it could mean that atherosclerosis is not a major cause of cardiovascular death. Despite the well-established premature atherosclerosis in patients with diabetes and the common notion that atherogenesis is accelerated in patients with uremia, there is no convincing evidence that dialysis patients with diabetes commonly die from atherosclerotic cardiovascular diseases. Indeed, the most common causes of cardiac death listed in the US Renal Data System (18) and the Hemodialysis (HEMO) Study (19) were sudden death, arrhythmia, and unknown. Nonischemic cardiomyopathy, such as left ventricular hypertrophy and cardiac fibrosis with or without heart failure, as well as electrolyte disturbance may be responsible for many of these arrhythmic or sudden causes of death, which is unlikely to be modified by the administration of statins.

A second potential explanation for the lack of clinical effect of atorvastatin in the 4D Study was the trend for the mean serum LDL cholesterol level to decrease in the placebo arm, approaching that of the statin arm, over time during follow-up. This decrease in LDL cholesterol level was likely due to patients'

violating the research protocol by taking statins (drop-in) in the placebo arm.

A third potential explanation is that statins are, in fact, effective in decreasing cardiovascular events in dialysis patients with diabetes, but the sample size of the 4D Study was not sufficiently large to detect the modest effect. According to this paradigm, treatment of patients with diabetes at this stage of CKD (stage 5D) may be too late, because statins seem to confer clinical benefits in earlier stages of CKD (15). If the effect size of statins in decreasing the cardiovascular composite end point in dialysis patients with diabetes is indeed 8% (RR 0.92 as shown in the 4D results), instead of the 27% that the study was designed for, then a much larger cohort would have been necessary to detect the modest effect.

Yet another potential explanation is that statins have adverse effects that counteract their beneficial effects. In the 4D Study, there was a two-fold increase in the RR for fatal stroke in the atorvastatin arm (RR 2.03; 95% CI 1.05 to 3.93; $P = 0.04$). This finding has been interpreted by some to be a potential harmful effect of statins. A biologically plausible mechanism by which statins increase fatal strokes is not apparent. In patients without uremia, including those with diabetes, statins in fact lower the incidence of stroke (3,4,13). Of note is that the number of fatal stroke events in the 4D Study was very small, with only 27 in the atorvastatin arm and 13 in the placebo arm; therefore, type I statistical error was prone to occur. In the same trial, atorvastatin paradoxically reduced the rate of all cardiac events combined (RR 0.82; 95% CI 0.68 to 0.99; $P = 0.03$); the event rates were much higher, with 205 in the atorvastatin arm and 246 in the placebo arm. It is unlikely that statins have opposite effects on these two organs, by harming the brain while protecting the heart. Nonetheless, a potential adverse effect of statins on stroke in dialysis patients cannot be absolutely ruled out.

A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events

A more recent randomized trial of statin on clinical outcomes in long-term hemodialysis patients is A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events (AURORA) (11). It was an international, multicenter, double-blind trial that randomly assigned 2776 long-term hemodialysis patients to either rosuvastatin (10 mg/d) or placebo. The combined primary end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, which was slightly different from that of the 4D Study. Three months after randomization to rosuvastatin, mean serum LDL cholesterol levels decreased by 43%. The magnitude of decrease was remarkably similar to that observed in the 4D Study of 42%, again confirming the pharmacologic efficacy of statins in this population.

During a median follow-up period of 3.8 yr in AURORA, there were no statistically significant differences in the primary end point (hazard ratio 0.96; 95% CI 0.84 to 1.11; $P = 0.59$) or all-cause mortality (hazard ratio 0.96; 95% CI 0.86 to 1.07; $P = 0.51$) between the statin arm and the placebo arm. Consistent with results from the 4D Study, there was also no significant effect of statin on the primary cardiovascular end point in the subgroup with diabetes. Furthermore, there was no relationship between the primary cardiovascular end point and serum LDL cholesterol levels measured at either baseline or 3 mo. In contrast to the 4D Study, however, secondary analysis showed no apparent differences in the risk for fatal stroke between the statin arm and the placebo arm in AURORA.

The major differences in the study design between AURORA and the 4D Study are as follows: (*1*) The AURORA enrolled approximately twice as many patients as the 4D Study; (*2*) approximately 74% of the AURORA patients did not have diabetes, whereas the 4D Study targeted patients with diabetes exclusively; (*3*) the 4D study was more generalizable from the age standpoint; the lower age limit of the 4D study was 18 yr, whereas the lower age limit of AURORA was 50 yr. Despite these differences, the remarkable similarity between these two trials was the apparent lack of efficacy for statins to decrease cardiovascular events in the long-term hemodialysis population.

Study of Heart and Renal Protection

As discussed already, *post hoc* subgroup analyses of large randomized trials suggest that, similar to the general population, statins are efficacious in decreasing cardiovascular events in stage 3 CKD, although the two randomized trials that specifically targeted long-term hemodialysis patients failed to confirm its efficacy in the latter population. These observations suggest that, at a certain stage in the progression of CKD, the phenotype has evolved from a clinically statin-responsive state to a clinically statin-resistant state. The ongoing Study of Heart and Renal Protection (SHARP) is the largest randomized trial to assess the effects of intense cholesterol-lowering pharmacotherapy in patients with CKD (20). It aims at studying the effects of the combination of simvastatin and the cholesterol-absorption inhibitor ezetimide by randomly assigning approximately 6000 patients with non–dialysis-dependent CKD and 3000 long-term dialysis patients. The primary outcome will be a composite of cardiac death, nonfatal myocardial infarction, nonfatal or fatal stroke, and revascularization.

Similar to AURORA but different from the 4D Study, SHARP has no specific lipid criteria for exclusion. There are at least two major differences between SHARP and these two completed trials. First, the majority of the SHARP participants had non–dialysis-dependent CKD at enrollment, with the lower serum creatinine limits of 1.5 μmol/L (1.7 mg/dl) for men and 130 μmol/L (1.5 mg/dl) for women. Among the study population with ESRD, both hemodialysis and peritoneal dialysis patients were included in SHARP. In contrast, the 4D Study and AURORA enrolled only long-term hemodialysis patients. A strength of SHARP is its potential to examine the efficacy of statins in various stages of CKD so that we can learn at which stage the CKD population generally becomes clinically resistant to statins. The distribution of GFR in the CKD study population in SHARP is unclear; however, unless there were a concerted effort to recruit patients with stages 4 and 5 CKD, most of the nondialysis patients with CKD were likely to have stage 3 CKD at the time of enrollment because of the much higher preva-

lence of individuals with less advanced kidney disease in the population (21). It is therefore uncertain whether there will be sufficient power in subgroup analyses to detect a statistical interaction between cholesterol lowering and CKD stage on clinical outcomes.

A second important difference between SHARP and the two completed trials is that SHARP excluded patients with a history of myocardial infarction and revascularization, although it is not strictly a primary prevention trial (20). In contrast, the 4D Study and AURORA included patients with these cardiovascular histories. This disparity needs to be taken into consideration should SHARP yield results that are different from these two completed trials.

Hypertriglyceridemia in Uremia

A potential explanation for the lack of efficacy of statins to decrease cardiovascular events in dialysis patients is the postulate that LDL cholesterol is not a major atherogenic factor in this population. For example, endothelial dysfunction is commonly observed in uremia, but it is not usually attributed to dyslipidemia. Even within the domain of lipids and lipoproteins, increased serum LDL cholesterol level is not a prominent feature in dialysis patients. Instead, hypertriglyceridemia is the hallmark of uremic dyslipidemia (22).

In normal individuals, plasma triglycerides are predominantly found in chylomicrons and very-low-density lipoproteins, which have the primary function of transporting fatty acids for energy consumption and storage in various organs. Triglyceride-rich lipoproteins accumulate in uremia (23,24), which is the consequence of both a high production rate and, more important, a low fractional catabolic rate. The decreased catabolic rate is likely due to the decreased activity of lipoprotein lipase and hepatic triglyceride lipase. The cause of the decreased lipase activities in uremia was reviewed (25). The primary physiologic function of these enzymes is the cleavage of triglycerides from lipoprotein particles. Thus, there are two major consequences of impaired lipase activities. The first is the decreased availability of free fatty acids for energy use and storage, which may contribute to the protein-energy malnutrition syndrome in dialysis patients. The second is the accumulation of chylomicron remnants and intermediate-density lipoproteins in the plasma as the result of incomplete catabolism of chylomicrons and very-low-density lipoproteins, respectively. Experimental and epidemiologic studies have strongly supported the notion that these remnant lipoprotein particles are highly atherogenic (26–28). Despite the modest increase in serum triglyceride levels in dialysis patients, which are usually in the range of 200 to 300 mg/dl, its contribution to atherosclerosis cannot be underestimated.

There is a paucity of data on the effects of hypertriglyceridemia on clinical outcomes in dialysis patients. Epidemiologic studies in the population without CKD, however, have demonstrated a relationship between serum triglyceride levels and the incidence of cardiovascular disease (29,30). Clinical trials aimed at decreasing serum triglyceride levels in the population without uremia have also shown beneficial clinical effects. For example, subgroup analysis of the Bezafibrate Infarction Prevention trial results showed that, in patients with serum triglyceride levels ≥200 mg/dl, there was a significant decrease in the risk for myocardial infarction and sudden death when their serum triglyceride levels were lowered pharmacologically (31).

HDL Cholesterol in Uremia

Low serum HDL cholesterol level is associated with cardiovascular disease in the general population. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) randomly assigned 2531 men who had a history of coronary heart disease and had low serum HDL cholesterol levels to either gemfibrozil or placebo (32). The composite outcome of nonfatal myocardial infarction and coronary death was significantly reduced in the gemfibrozil arm. Furthermore, HDL cholesterol levels were inversely related to coronary events in that trial. *Post hoc* analysis of that trial showed that gemfibrozil was also associated with a reduction in coronary events in the subgroup of patients with creatinine clearances of 30 to 75 ml/min (33). Low serum HDL cholesterol level is also a characteristic feature of uremic dyslipidemia. Low serum HDL cholesterol levels, in particular the levels of HDL_3, diminish the reverse transport of cholesterol from peripheral cells to the liver, thereby burdening the vasculature with cholesterol and promoting atherosclerosis. Another consequence of low serum HDL cholesterol is decreased paraoxonase activities, thereby allowing the oxidation of LDL to proceed.

The cholesteryl ester transfer protein (CETP) facilitates the transfer of cholesteryl ester from HDL to other lipoproteins (34). Thus, CETP inhibitors should increase serum HDL cholesterol levels and theoretically decrease cardiovascular diseases. The administration of the CETP inhibitor torcetrapib indeed increases HDL cholesterol levels in patients without uremia; however, a large clinical trial showed an unexpected increase in cardiovascular events and all-cause mortality in patients who were treated with torcetrapib in addition to atorvastatin, compared with atorvastatin alone (35). This adverse outcome might have been related to an increase in BP associated with torcetrapib that is independent of its lipid-directed effects (36). It is conceivable that other molecules that increase HDL cholesterol—but without the BP effect—may have beneficial clinical effects on patients without uremia and dialysis patients, but clinical trial results of those compounds are not available.

Other Dyslipidemic States in Uremia

Although serum LDL cholesterol levels are not typical high, there are often qualitative changes in LDL in dialysis patients. For example, the proportion of small dense LDL (sdLDL) is often increased (37). sdLDL is a subtype of LDL that has high affinity for macrophages, has high propensity to penetrate the vessel wall, becomes oxidized, and triggers the atherosclerotic process. LDL particles can also be modified in other manners that promote atherosclerosis. A notable modification is oxidation, which seems to be enhanced in uremia (38). Carbamylation, the modification of proteins including LDL by the urea-derived cyanate moiety, is unique to the uremic state (39). Both oxidized LDL and carbamylated LDL possess cell-directed

properties that are proatherogenic. Although statins undoubtedly decrease serum LDL cholesterol levels, their effects on the various forms of modified LDL particles in dialysis patients are far less clear.

Serum levels of Lp(a) are also increased in dialysis patients (40). Lp(a) is an LDL-like lipoprotein that consists of a covalently bound apolipoprotein(a). High serum Lp(a) level is a cardiovascular risk factor in the general population (41). High serum Lp(a) levels and the low molecular weight apolipoprotein(a) phenotype have been associated with adverse clinical outcomes in dialysis patients (42,43).

In summary, the hallmarks of uremic dyslipidemia are hypertriglyceridemia, increased remnant lipoproteins (chylomicron remnants and intermediate-density lipoproteins), reduced HDL cholesterol and altered HDL isoform distribution, increased sdLDL and modified LDL, and increased Lp(a). Significantly elevated plasma LDL cholesterol level is not a typical feature. There are various degrees of evidence supporting the atherogenic roles of these dyslipidemic phenotypes, and many of them are not amenable to treatment with statins.

Considerations for Treatment of Dyslipidemia in Dialysis Patients

Nephrologists are faced with a dilemma when confronted with the decision to prescribe or withdraw statins from dialysis patients. On the one hand, it may be difficult to forsake the common dogma of prescribing statins to patients with enormously high cardiovascular risks. On the other hand, we are struck with the lack of evidence of the efficacy of statins in preventing cardiovascular events in this population. After all, if we do not believe in data that are generated in randomized trials, then there would be little reason to perform these labor-intensive and expensive trials in the first place. In an effort to justify our use of statins in the dialysis population, we have scrutinized the study design and results of the randomized trials more critically.

The generalizability of all clinical trials is limited by their inclusion and exclusion criteria. We have discussed the restriction of the 4D Study to dialysis patients with diabetes and the exclusion of dialysis patients who were younger than 50 yr in AURORA. Thus, we can perhaps rationalize the use of statins in dialysis patients who do not have diabetes and are younger than 50 yr. We can also rationalize the use of statins for primary prevention, because both the 4D Study and AURORA included patients with clinical cardiovascular diseases, such as the history of myocardial infarction, as part of their respective cohorts. The rationale for this paradigm would be the postulate that if these trials were designed for primary prevention, then they would have yielded positive results because patients with known clinical cardiovascular diseases beyond remedy would have been excluded.

Perhaps a more reasonable subgroup of dialysis patients for whom the prescription of statins should be considered is those with moderately to very high serum levels of LDL cholesterol. The 4D Study excluded patients with LDL cholesterol >4.9 mmol/L (190 mg/dl). Thus, only approximately 13% of the randomly assigned patients had serum LDL cholesterol levels >160 mg/dl at baseline. Cholesterol levels were not part of the exclusion criteria in AURORA; however, the baseline serum total cholesterol and LDL cholesterol levels of the cohort were only approximately 175 ± 35 and 100 ± 42 mg/dl, respectively. That means that only approximately 16% of the randomly assigned patients had serum LDL cholesterol levels >142 mg/dl at baseline. Thus, many patients who had high LDL cholesterol levels could have been excluded if the primary physicians or the investigators believed that they should be treated with statins and were therefore reluctant to subject them to randomization in the trial. On the basis of these exclusion criteria and baseline characteristics of the cohorts, it would be reasonable to make the supposition that the effects of statins on clinical outcomes in patients with moderately to very high LDL cholesterol (>150 mg/dl) were not adequately examined and are therefore unknown. Thus, initiating statins for these patients is reasonable, pending additional data in the future.

Another argument in favor of prescribing statins to dialysis patients is the seeming lack of excessive adverse effects or events, compared with placebo controls (10,11), the increase in fatal stroke in the 4D Study notwithstanding. Finally, neither the 4D Study nor AURORA directly examined the clinical effects of withdrawing statins from dialysis patients. Hence, these studies did not provide guidance on whether statins should be withdrawn for patients who are already taking these drugs.

In addition to statins, other drugs are available to modify serum lipid profiles. There are some data on the pharmacologic effects of these nonstatin drugs, but randomized trials of reasonable sizes to address their efficacies in modulating hard clinical outcomes are lacking. Although there is a theoretical basis for the treatment of hypertriglyceridemia for cardiovascular protection, no randomized trial data are available to determine the efficacy of this approach in dialysis patients. At present, the threshold for the pharmacotherapy of hypertriglyceridemia in dialysis patients is high, probably around serum total triglyceride levels of 500 mg/dl. ω-3 fatty acid, gemfibrozil, or nicotinic acid can be used to treat hypertriglyceridemia. Nicotinic acid is particularly valuable, because it also increases serum HDL cholesterol level and lowers serum LDL cholesterol, Lp(a), and sdLDL levels (44,45). An increased risk for myopathy seems to be associated with fibrates in patients with CKD (46). Special caution is particularly warranted when fibrates are used in conjunction with statins.

The use of antioxidant pharmacotherapy has strong theoretical basis for its effects on both lipoproteins and nonlipoprotein molecules. A strong rationale for the use of antioxidants is that dialysis patients are generally in a state of high oxidative stress (47). A beneficial effect of vitamin E on the oxidative susceptibility of LDL cholesterol in dialysis patients has been demonstrated (48). Two small randomized trials that used vitamin E (49) and N-acetylcysteine (50), respectively, showed a decrease in cardiovascular events, although total mortality was not affected significantly. Hemodialysis using a vitamin E–coated membrane resulted in the reduction of serum oxidized LDL levels and an attenuation of the increase in aortic calcification index (51). Increasing serum HDL cholesterol by regular exer-

cise is a sensible therapeutic approach, but dietary manipulation of serum lipids needs to take into account its potential for promoting malnutrition.

Conclusions

Serum total cholesterol and LDL cholesterol levels are typically not high in long-term hemodialysis patients. Despite substantial lowering of LDL cholesterol levels, no convincing evidence of clinical benefits or harm is associated with statin use. Other dyslipidemias, such as the accumulation of triglyceride-rich lipoprotein remnant particles, may be more atherogenic in uremia. Future research should focus on the more widespread use of assays for various lipids and lipoproteins that are abnormal in uremia, as well as the epidemiology and therapy of these other dyslipidemic states. Inasmuch as the causes of cardiovascular diseases in dialysis patients are multifactorial, the treatment of a multitude of these risk factors is likely to be necessary to produce substantial improvements in clinical outcome.

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Disclosures

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